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ADRENAL-SYMPATHETIC SYNDROME

CHROMAFFIN TISSUE TUMOUR WITH PAROXYSMAL HYPERTENSION

BY

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From St. James' Hospital, London

Received May 21, 1943

The chromaffin cells of the adrenal medulla are a part of the scattered " chromaffin tissue system." The tumours of these cells, the pheochromocytomata or adrenal paragangliomata are nearly always benign, but usually produce paroxysmal hypertension ending fatally if the tumour is not removed.

There are reports of 152 cases of pheochromocytoma. The only extra-adrenal paragangliomata that have produced the hypertensive picture are those arising in the retroperitoneal tissues between the kidneys : of 13 such cases, 9 had the cardiovascular syndrome typical of the adrenal cases, and they form part of one clinical problem and are considered with the adrenal cases here. Of these 165 cases, 90 have been described since 1929, and 36 operations have been reported.

Paragangliomata arising from the intrathoracic sympathetic chain, from below the bifurcation of the aorta, from the coccygeal body, from the carotid body, and in the wall of the intestine are described, but very few of these are true tumours of the chromaffin tissue system (Da Costa, 1939–40; Christie, 1933) and none has given the cardiovascular picture.

In 1886 Frankel reported an autopsy finding of bilateral adrenal tumours and cardiac hypertrophy in a girl of 18 who for three years had had attacks of palpitation, headaches, and vomiting. The first full clinical description was by Labbé, Tinel, and Doumer (1922) who observed the paroxysmal hypertension in the attacks. The first case in which the correct diagnosis was made and followed by operation and cure was that of Pincoffs and Shipley (1929).

The final important step was by Beer, King, and Prinzmetal (1937) who showed that during the crises the blood contained large amounts of adrenaline.

Incidence and pathological anatomy. The incidence of pheochromocytoma in men and women is equal. Cases with the cardiovascular syndrome occur at all ages; mostly between 20 and 50 years. The association with generalized neurofibromatosis is recorded in nine cases.

The common lesion is a benign adenoma of one adrenal body. Sixteen bilateral tumours are recorded: of these, 8 showed a cardiovascular syndrome and 6 were malignant. Malignant pheochrome tumours are rare (15 cases), but may show a hypertensive picture. In about one case in ten the tumour is extra-adrenal, lying between the adrenal and the midline.

In size the tumour is usually like an orange, but tumours weighing from 13 to 2000 grams are described. The surface is often bossy and a line of remnants of cortical tissue is common. On section there are usually hæmorrhagic cysts set in fibrous tissue.

Histology. (See Geschickter (1935) for good illustrations and Edwards (1937) and van Goidsenhoven and Appelman (1934) for methods of staining.) The commonest picture is of polyhedral cells of notably varied size and shape arranged in alveolar masses separated by fibrous septa, resembling cirrhotic liver with hyperplasia. The abundant cytoplasm is finely granular and the nucleus round or oval with a single nucleolus. Multinucleated giant cells and syncytial sheets of cells are sometimes seen. Occasionally there are groups of cells resembling lymphocytes. The cells may be arranged round vascular spaces giving pseudo-rosettes (Peyron, 1930).

In tissues fixed with chrome salts the characteristic chromaffin reaction is seen. The brown granules may be seen in the cytoplasm or nucleus, or in the stroma.

Adrenaline in tumours. That these tumours give strongly positive reactions to chemical tests for adrenaline (Edwards, 1937) was shown thirty years ago. These results have now been confirmed by demonstrations of a pressor principle behaving like adrenaline. The quantitative estimations vary from 0·12 up to 20 mg. (Belt and Powell, 1934) per gram of tumour tissue (normal adrenal medulla about 0·4 mg.).

Association of other adrenal body tumours with hypertension. Paroxysmal hypertension has been reported with adrenal ganglioneuroma (Rogers, 1933), with neuroblastoma (Ernould and Picard, 1934) and with cortical tumours (Rimbaud and Delmas, 1939; Plazy and Germain, 1932). Persistent hypertension has been found with retroperitoneal ganglioneuroma (Jergensen, 1933), with an adrenal

" sympatheticoblastoma " (Binger and Craig, 1938) and is, of course, not uncommon with adrenal cortical tumours.

Two cases are here reported, one fully and one more shortly, and this is followed by a general discussion of the clinical picture, diagnosis, and treatment.

Reports of Two Cases

An aircraftman, aged 29, awoke one morning with profuse sweating, pain across the epigastrium, and vomiting. These continued and on the third day he felt very ill and was sent to hospital. There was no palpitation. He had never had any illness like this before.

On admission he was in a state of collapse. The extremities were blue and cold. His mouth temperature was normal. The pulse was 80, tiny, but hard; the blood pressure, 197/167. No signs of disease were detected in the heart or lungs. There was herpes febrilis of the lip and vague tenderness of the right side of the abdomen. The urine showed a trace of albumen.

He was treated with warmth, rest, morphine, and fluids by mouth. There was no further vomiting and he improved steadily. Next day he felt and looked much better; the following day the blood pressure was 125/100, and a provisional diagnosis of paroxysmal hypertension from adrenal medullary tumour was made.

Previous history. The family history was of no significance. Up to 25 years of age he was healthy save for insomnia at times and, at 22, a right-sided orchitis, which left the testicle atrophic.

From the summer of 1937, that is, for four years, nearly every morning shortly after getting up, he had a few minutes' nausea, usually accompanied by palpitation, but without vomiting. After this nausea passed off he felt weak for 10 to 15 minutes.

In July, 1938, he had an attack of thumping of the heart—the rate and rhythm being unaffected. Later that summer for half one day he felt ill and for a week after had severe headache and felt weak.

From November, 1938, to April, 1939, he had severe headaches. Three weeks after they started he began to have attacks of thumping of the heart during which the headache was worse. He was in St. Thomas's Hospital in December, 1938, and while in bed there the palpitation recurred frequently, the forcible beat of the heart being visible from several feet away. No signs of organic disease were found, except that the blood pressure was 144/100. The palpitations continued for a time sometimes accompanied by choking feelings and vomiting. After they ceased the headaches gradually cleared up.

At the end of 1939 and occasionally since he noticed that sometimes when leaning to the left he would suddenly feel nervous and dizzy.

In July, 1940, he joined the R.A.F. Sometimes, during the next winter, he had a momentary feeling of intense weakness in the legs while walking. In February, 1941, at a medical examination for aircrew he says that his blood pressure seemed to arouse interest; at a re-examination it was 120/70 and he was passed.

During the summer of 1941 on several occasions at drill he was told he was pale. Only sometimes was this pallor accompanied by subjective feelings of trembling, anxiety, and faintness, lasting up to half a minute. Later these sensations occurred about twice a day and he also noticed that crouching would bring them on.

In July, 1941, the severe paroxysm described led to his admission to hospital. While there he had some further minor crises which may be conveniently described here.

One afternoon he was observed to be pale. He said he felt well but had just been passing water which since cystoscopy, for which a meatotomy had been needed, had been painful. His blood pressure was found to be 210/135; ten minutes later it was 150/105 (at rest at this time it varied from 120/95 to 130/110). This was evidently a symptomless paroxysm of hypertension induced by painful micturition. Similar attacks were observed on succeeding days.

During the perirenal pneumography a second insufflation gave severe pain. He became very distressed, complaining of suffocation; his face was congested and his blood pressure was 240/170. This attack lasted about ten minutes and was followed by prostration for half an hour.

Progress in hospital and investigations. Two days after admission he looked and felt well. For the next two weeks, however, he had a symptomless pyrexia, often from 99 to 100·6° F., for which no cause could be found.

Psychologically the patient was a placid, well-balanced person without conscious anxiety feelings and of normal sexuality.

X-ray of the chest showed no disease of heart or lungs, but a dextrocardia with transposition of viscera was revealed. The teeth were healthy. The blood two days after admission showed R.B.C., 5·0 million; Hb. 98 per cent (Haldane); W.B.C., 21,200 (neutrophils 82 per cent, lymphocytes 11 per cent, monocytes 7 per cent), and eleven days later Hb. 85 per cent, W.B.C. 8000 (neutrophils 75 per cent). Blood chemistry (20/9/41) gave serum chloride as sodium chloride 560 (normal 560–

620), sodium 326 (normal 325–350), potassium 46 (normal 16–20) mg. per 100 c.c.—a very significant rise in potassium level..

A rounded tender mass was palpable high up in the left loin. As the pyrexia abated this mass seemed to become less easily felt and less tender. Repeated examinations of the urine revealed only an occasional trace of albumen; its specific gravity ranged from 1024 to 1001 in tests, and the urea clearance was 113 per cent normal. X-ray showed no renal stone, and cystoscopy a normal bladder. Intravenous pyelography showed the left kidney slightly depressed with a little deformity of the upper calyx.

Attempts to induce attacks by the various manœuvres described below were made but none of these affected the blood pressure level. As noted above, for a few days after cystoscopy he had symptomless paroxysms of hypertension induced by the dysuria. These were an important confirmation of the diagnosis. Adrenaline was given intramuscularly. The pressure which was about 160/120 before the injection was little affected by 0·25 c.c. of 1/1000 solution, but after 1·0 c.c. it rose to 205/140 for a few minutes. As the rise began the patient said it was like the beginning of an attack. On another day 1·25 c.c. gave pallor and palpitation but only a slight rise of pressure. A cold pressor test (Hines and Brown, 1933) gave a " positive " result, the pressure rising from 135/100 for 3½ minutes to reach 160/120 with a slower fall.

The electrocardiographic findings are given later (see p. 7).

Operations and progress. Mr. L. R. Broster kindly agreed to operate and it was decided to do an exploratory laparotomy and to remove the tumour by the lumbar route at a second operation.

The evidence obtained from a *perirenal pneumography* by Mr. G. C. Sawyer was too indefinite to help in deciding the side of the tumour. Also, the insufflation on the right side was painful and led to an unpleasant attack.

At an exploratory laparotomy a tumour the size of a tangerine orange was found above the left kidney. The right adrenal body was normal. The blood pressure which before the operation had been rising from 130/108 to 150/112 was after induction 180/120 and remained there throughout, being unaffected by squeezing the tumour. The pulse, 110 and regular at first, soon became irregular in force and after manipulation of the tumour there was an irregular tachycardia (rate 200) for ten minutes. This may have been due to the use of cyclopropane in the presence of excess adrenaline (Burstein *et al.*, 1940). There was no disturbance after the operation and no significant change in the white blood count two days later.

The tumour was removed two weeks later on 24/9/41, under gas-oxygen-ether preceded by omnopon-scopolamine.

For combating the expected fall in blood pressure after removal of the tumour, a 1/100,000 solution of adrenaline HCl in normal saline was prepared. When the patient was anæsthetized a slowly running continuous intravenous drip of normal saline was inserted with provision for switching over to the adrenaline solution if necessary. This drip was kept going during and for some hours after the operation. The tumour was removed through a lumbar incision. The blood pressure, 175/110 at the beginning, rose during the operation to 225/145, and fell to 90/70 in ten minutes after the removal of the tumour. About 10 c.c. of the adrenaline solution restored it to 120/80 for ten minutes, but for some hours after the operation it was about 80/60 and the patient was slightly cyanosed and sweating profusely. The day after it was 140/105, settling on the third day to 130/95. He was given sodium desoxycorticosterone for three days.

He made an uninterrupted recovery and was discharged three weeks later, having had no recurrence of the minor symptoms that were previously of daily occurence.

When he was discharged, though he was free of infection his white count was still raised, 17,500, neutrophils 78 per cent (the day after the operation it had been 23,000 and 77 per cent). He went to an R.A.F. hospital, and while there he had four minor attacks, and then no further attacks in a year. As the tumour was histologically malignant he was given deep X-ray therapy six months after the operation. He returned to civil life and is working very hard. His weight is well maintained and he writes that he is fit and entirely free of any of the symptoms he had before the operation. This was confirmed by an examination at which his blood pressure was normal.

Description of tumour. The tumour was a flattened ovoid 5·5 × 4·5 × 2·5 cm., weighing 63·5 grams. The surface showed bluish bosses and a line of cortical remnants (Fig. 1). Section showed a fibrous capsule surrounding a matrix which was hard and pearly white in the centre and in which were set round areas of purplish fleshy tissue corresponding to the bosses on the surface (Fig. 2). There were two irregular areas of yellow tissue.

Histology (Dr. H. W. C. Vines). The tumour has a well defined fibrous capsule, into which the tumour cells appear to be infiltrating to some extent. Some lymphatic spaces contain tumour cells.

The tumour is composed of large polyhedral cells, many compressed into spindle cells. There are a few multinuclear cells and some with deeply staining pyknotic nuclei. Mitoses are rare. There are small areas of necrosis with replacement by very loose areolar fibrous tissue; and areas of

FIG. 1.—Case 1. Drawing of tumour, slightly under actual size. The line of cortical remnants and the bosses are visible.

FIG. 2.—Case 1. Section across tumour, slightly under actual size. The fibrous capsule, the fleshy cysts, pearly fibrous matrix, and two areas of yellow fatty tissue are seen.

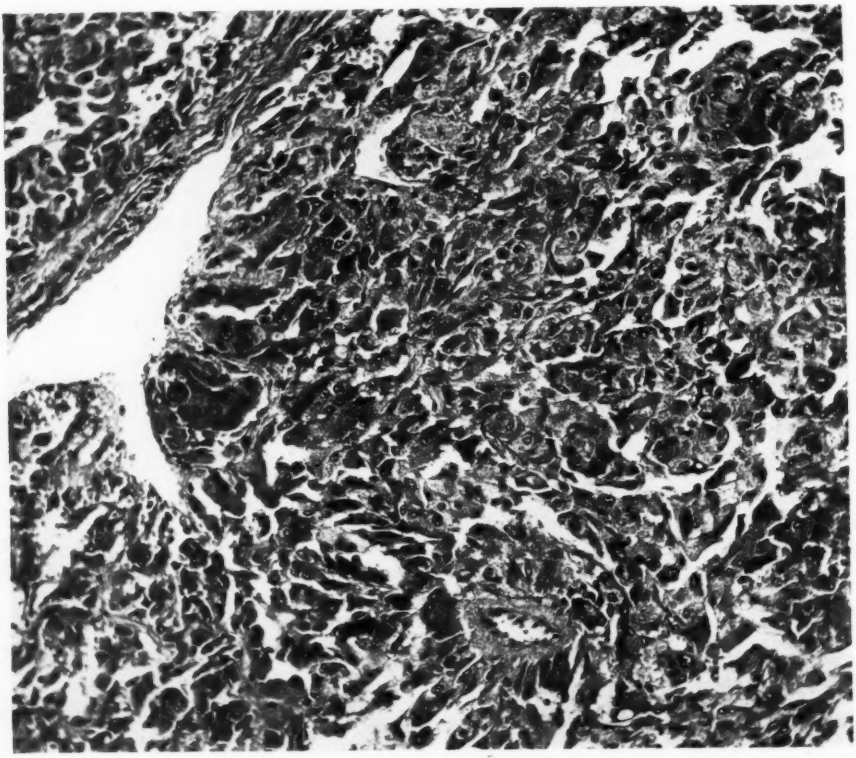

FIG. 3.—Case 1. Microphotograph; × 175; Hx and E. Showing cells of varied shapes and sizes; giant cells visible by the cleft; and at bottom perivascular arrangement of cells.

hæmorrhage. The vessels are numerous and many are thin-walled but not sinusoidal. There is some patchy deposit of hæmosiderin. In some areas perivascular survival of the tumour cells presents the appearance of pseudo-rosettes, or of a papilliferous arrangement. The tumour cells give a chrome reaction (Fig. 4). The growth does not appear entirely benign. It may be called a pheochromoblastoma.

Adrenaline content (Dr. Derek Richter and Dr. F. C. MacIntosh). This was done on an extract made of a slice across the tumour. By colour reaction with iodine, the adrenaline content was 5·25; and by biological test on atropinized eviscerated cat, 8 mg. per gram of wet tumour tissue (normal adrenal content 0·4 mg. adrenaline per gram.).

Case 2. Short notes of a case which came to my notice during the preparation of this paper, are included. A clerk, aged 25, was invalided out of the Army in 1940 for "heart trouble." He had

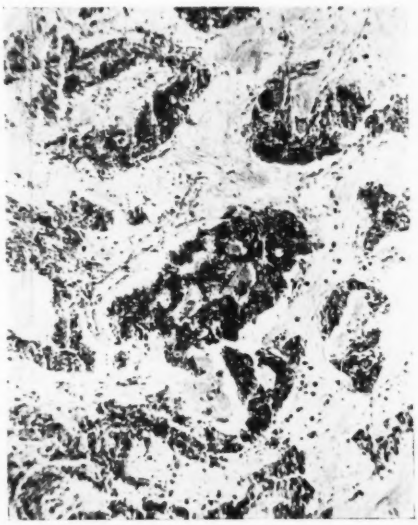

FIG. 4.—Case 1. Microphotograph, chrome-fixed and unstained showing "lobules" of chromaffin cells set in fibrous stroma. Magnification × 62.

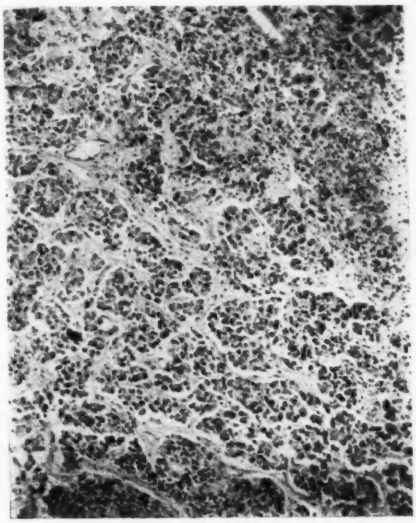

FIG. 5.—Case 2. Microphotograph (Hx and E), showing "lobules" of cells in fibrous stroma. Magnification × 66.

been breathless on exertion, with a few attacks of nocturnal dyspnea. There was no history of nephritis.

One night he developed severe breathlessness. His doctor gave him morphia and sent him to hospital. On arrival he was very cyanosed with audible bubbling respiration and was bringing up a blood-stained froth. There was no overfilling of the veins and no œdema of the ankles. In the chest many crepitations and bubbling noises were heard. His blood pressure was 160/120. The blood urea was 40. He was given oxygen, atropine, and later morphia, but he failed to improve and died nine hours after admission.

At autopsy, both lungs were grossly congested. The heart was of average size, the right auricle dilated, the left of normal size; the mitral valve admitted three fingers. The vessels were normal. The liver showed acute congestion only; the kidneys and the other organs were normal excepting the right adrenal body. This was rounded and enlarged, about 2 inches in diameter. On section there was towards the periphery a large cyst filled with blood and tumour tissue. Histological examination showed normal left adrenal and kidney. The right adrenal showed alveolar masses of polygonal and polymorphic cells in a fibrous stroma (Fig. 5). Chrome staining was not done.

CLINICAL PICTURE

Chromaffin cell tumours of the adrenal medulla may give—(i) Recurrent paroxysms of generalized vasoconstriction accompanied by a remarkable but transient hypertension; the *adrenal sympathetic syndrome*, (ii) Chronic hypertension with renal and cardiac failure, resembling malignant hyper-

tension, (iii) Addison's disease from local pressure on the cortex, an uncommon picture, or (iv) No symptoms. The descriptions given here deal chiefly with the first type which is the commonest, most easily recognized, and most treatable one.

The history of attacks usually extends over several years, even as long as 16 years (Allen, 1940). But they may end fatally after a few months or even days (Edwards, 1937). Sometimes there is a steady progress from mild occasional attacks to frequent and severe ones, but attacks may cease for a time, even for ten years (Hamilton, 1940). At first the blood pressure level is normal between paroxysms, but later these are often superimposed on a persistent hypertension. This may already be present at the earliest examination and occurs in about half the cases of long duration.

The first attack may be severe, but more often the early ones are mild. Or there may have been transient malaise, headaches, nausea, digestive troubles, diverse pains, dizzy spells, palpitations, the significance of which is not realized until a more severe paroxysm occurs. If the condition is not treated these major crises recur. The paroxysms vary in severity and clinical picture but in individual subjects they are often of one type. They may recur irregularly at long intervals, or several times a day, or daily at a set time.

Precipitating factors. Where attacks occur before breakfast, fasting may be a factor, but it is as common for them to occur after meals. Constipation may induce the vascular crises (Foucar, 1939). More easily understood as precipitating causes are exercise and emotion. Pain led to attacks in the present case. Drinking 1500 c.c. of water caused one fatal paroxysm (Howard and Barker, 1937). Attacks occur at operation, even before manipulation of the tumour. By far the commonest precipitating factors are postural, e.g. bending the trunk, combing the hair, etc. Where flexion of the trunk leads to attacks there is usually a palpable tumour, but it is not always flexion to the side of the tumour that provokes them. A steady pressure for two minutes to the adrenal region or to a palpable tumour may induce a paroxysm at once or after a few minutes (MacKenzie and McEachern, 1938). A sharp blow on the abdomen, warming the renal region, pressure on the carotid sinus, and the cold pressor test are other reported methods that may be tried in a suspected case.

But it is to be noted that in half the cases no special precipitating factors have been recorded.

The paroxysms. The recurrent vascular crises are the most important feature of the clinical picture. There is a sudden generalized vasoconstriction producing symptoms and signs from many parts of the body and so causing a characteristic picture. Less commonly patients may complain of symptoms limited to one system, e.g. of recurrent epigastric pain and vomiting or recurrent headache. The accompanying rise of blood pressure shows that it is the symptoms and not the vasoconstriction that is limited in distribution. A more detailed history or examination may yield other evidence of the widespread vasoconstriction. Symptomless paroxysmal rises of blood pressure have been noted by four authors.

Preceding the attack, there may be paraesthesiæ or an indefinable malaise which the patient recognizes as the aura of his attack. The commonest first symptom is palpitation, but various feelings in the extremities, epigastric pain, sinking feeling or nausea, substernal constriction or cardiac pain, lusty sneezing (in three cases), throbbing in the temples, dizziness, headache, or a sensation of shakiness or languor may mark the onset of the paroxysm. As it proceeds some or all of these symptoms may develop. A progress of symptoms upwards from the feet is described in several cases, when warmth or tinglings of the feet may be succeeded by cramps in the calves and thighs, then by abdominal colic and epigastric pain with nausea and vomiting, followed by thoracic angina radiating to the arms, then fullness, choking or pain in the neck, throbbing in the temples, dizziness, and finally an atrocious headache. Nausea is described in nearly all attacks and vomiting in most of them; and epigastric discomfort is often noted. Pain in various sites, severe headache, and vertigo are common. Sweating, a sense of hair-pulling (Nuzum and Dalton, 1938), lachrymation, and salivation are symptoms of pharmacological interest. Where the attacks are severe, spitting of blood (from acute pulmonary œdema) may be described. In other cases a condition resembling shock or collapse occurs.

In these major paroxysms the patient is obviously ill. The face is usually pale and anxious, but may be congested or blotchy or may alternate between pallor and redness. Coldness of the extremities is described in nearly every case; usually blanched, the hands may be purplish. A moderate rise of body temperature is common. The pulse is not infrequently noted as being weak or small; in the present case it was tiny but hard. The pulse rate may be up or down and may react differently in different attacks, or variably during one attack. Rhythm irregularities may occur. The heart beat is very forcible and may shake the bed. The second sound at the aortic area is loud and ringing; a transient aortic diastolic murmur may be heard at the height of the paroxysm (Bernal, 1933).

The systolic pressure may rise in a few minutes from 120 to over 300 mm.; and the diastolic in proportion. The level may vary widely during the attack. An initial apnœa or tachypnœa may be seen. An abdominal tumour, not always in the loins, is palpable in about one third of cases; it

may be, in fact, a kidney pushed down by the adrenal tumour. Other common signs are swelling of the neck veins and dilatation of the pupils. During the attack there may be anuria or oliguria with albumen and casts in the urine, and azotæmia, which may exceed 150 mg. urea per 100 c.c. Hyperglycæmia and glycosuria are common. The white blood cell count shows a rise due entirely to rise in lymphocytes, the percentage of which rises 25 or 30 per cent (MacKenzie and McEachern, 1938; Hatieganu *et al.*, 1939.)

Demonstration of excess of adrenaline in the blood. The first success was by Beer, King, and Prinzmetal (1937) perfusing the eviscerated rabbit's ear. Strombeck and Hedberg (1939) using a chemical method demonstrated a 30 times normal adrenaline content in the blood between attacks, with a 1000 times normal content in the attack. Earlier workers and also Biskind *et al.* (1941) were unable to find any pressor substance in the blood.

Duration and termination of paroxysms. The attacks may last minutes, hours, or days. The common length is one to two hours. The end of the attack may be marked by flushing of the face and neck, and abundant sweating, sometimes with salivation, lachrymation, and dilatation of the pupils. The blood pressure falls and after short attacks may reach a normal level in a few minutes.

After the paroxysm there is commonly a feeling of extreme prostration lasting from a few minutes up to several hours. Headache usually persists for some time after the attack.

Localized and minor paroxysms with symptoms of limited distribution are common; in these, however, closer investigation will often give evidence of symptoms or signs involving other systems.

Labbé, Tinel, and Doumer's patient attended for daily bouts of vomiting; Shipley's had diarrhœa and vomiting. Periodic nausea, headache, and abdominal pain immediately or an hour or two after meals, may be attributed to dyspepsia.

Angina pectoris is a common symptom and may be the most prominent. Palpitation may be the only complaint. Acute pulmonary œdema is not rare and in this disorder it may occur in the absence of cardiac enlargement or coronary artery disease. Shock or collapse may occur, as in the present case. In another case, during a paroxysm lasting three days, and giving a clinical picture of shock, the blood pressure varied between 90/70 and 240/150 without change in the general condition (van Goidsenhoven and Appelman, 1934). The cases resembling malignant hypertension are discussed below.

Severe headache, alone or with vomiting; and transient vertigo may occur by themselves. Transient loss of consciousness has been recorded in five cases, but all of these had persistently raised blood pressure. Periods of fatigue, lassitude, or weakness may be the salient feature (Fein and Carman, 1937; Hegglin and Nabholz, 1937). Sensations of anxiety may be the cause of consulting a physician (Palmer and Castleman, 1938).

Cases with lumbar pain and abnormal urinary findings; with recurrent glycosuria resistant to insulin; with bouts of malaise and pain; or with congestion of the face combined with profuse sweating; and other minor attacks are unlikely to be elucidated unless paroxysmal hypertension is found to accompany the symptoms, or a major crisis occurs.

Between attacks. Many subjects enjoy good health in the intervals. Loss of weight and anæmia (rarely severe) are common, and a persistently raised blood pressure is found in half the cases. Neutrophil leucocytosis, dyspepsia, or obstinate constipation may be seen. An abdominal tumour is present in one case in three. Fever occurs rarely. Lassitude or insomnia occur but anxiety is surprisingly rare.

The mode of death. The commoner modes of death after paroxysms are acute pulmonary œdema, shock or collapse, and cerebral hæmorrhage. Collapse may follow parturition or a minor operation under local anæsthetic (5 cases), or a major operation. Death with high fever is described. Chronic renal failure, Addison's disease, and malignant cachexia are rarer causes. Five cases have died suddenly and unexpectedly in hospital while undergoing investigation or awaiting operation.

Persistent hypertension. Some cases of pheochromocytoma from the start closely resemble malignant essential hypertension. Others have been followed from a stage in which hypertension occurred only in the attacks to a second stage of continuous hypertension with its usual sequelæ. The paroxysms may continue. If they do, symptoms are usually less widespread. Albuminuria, cylinduria, and azotæmia are common but may vary remarkably independently of the patient's symptoms. Even after it has been high for a long period, the blood pressure may fall to normal for a time (van Goidsenhoven and Appleman, 1934).

Electrocardiographic changes during attacks. Auricular premature beats (Rogers, 1933), runs of tachycardia of auricular and ventricular origin (Pincoffs, 1928), and sinus bradycardia with beats arising alternately from S-A and A-V nodes (Burgess *et al.*, 1936, Hegglin and Holzman, 1937) are recorded. A rapid arrhythmia during operation was seen by Hatieganu *et al.* (1939) and in the present case. QRS slurring (Allen, 1940) and left axis deviation (Kremer, 1936; Rogers, 1933) are recorded. The T wave varies; it may be very high (Pincoffs, 1928; Burgess *et al.*, 1936), flattened (Hegglin and Holzman, 1937), or inverted in leads I and II (Kremer, 1936; Allen, 1940; Rogers, 1933).

After attacks a remarkable lengthening of the S–T interval and variable changes in the T waves lasting a few days after severe attacks were noted by Hegglin and Holzman (1937). In the present case there was inversion of T in all leads lasting for some weeks after the attack. Neither inversion of T in all leads nor such slow recovery is described elsewhere.

Between attacks a normal curve was found in 6 of the 18 cases with reports. Very large P waves were noted in 3 cases, but left axis deviation and diminution or inversion of T were the most common findings. In the absence of repeated examinations it is not certain how permanent these changes were (cf. present case).

Where repeated curves have been taken (Rogers, 1933; Hegglin and Holzman, 1937) there have been notable variations in different attacks. The commonest change seen is flattening or inversion of the T wave in leads I and II. In two cases there was increased prominence of T waves. Experimentally adrenaline, usually but not always, gives increased T waves. The changes in rhythm seen in attacks are probably the resultant of A-V node acceleration from adrenaline and S-A node slowing due to the vagal effect from the depressor reflex. The T wave flattening seen in attacks is probably similarly a vagal effect. The S–T and T variations lasting for a few days after severe attacks observed by Hegglin and Holzman (1937) were considered to be due to metabolic upset in the myocardium. Similar temporary T wave depression may occur for a few days after a bout of paroxysmal tachycardia. The acute hypertension of acute nephritis may be associated with temporary changes in the T wave lasting some weeks. (Master, Jaffe, and Dack, 1936; Langendorf and Pick, 1938). These alterations, which are not exactly parallel to the rise in blood pressure, are probably partly due to the hypertension and partly toxic.

In the case reported here, Fig. 6A, taken a week after admission, showed dextrocardia, left axis

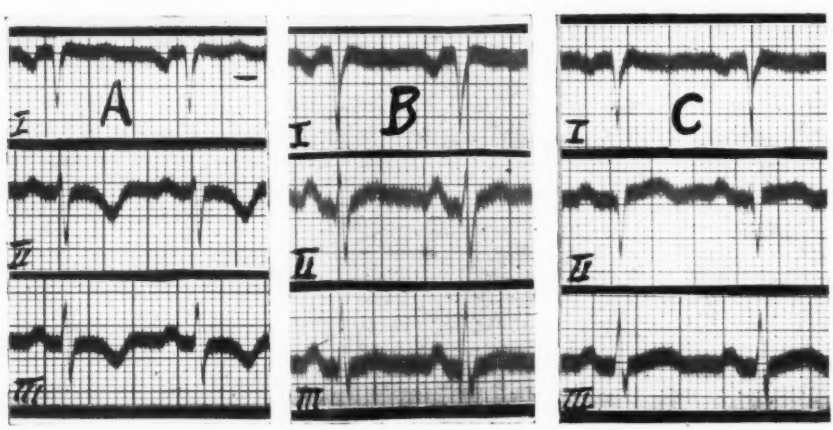

FIG. 6.—Case 1. Electrocardiograms: (A) 1 week after admission (8/7/41). (B) 8 weeks after admission (25/8/41). (C) Shortly before operation (20/9/41).

deviation, and inversion of T in all leads. These changes were still present three weeks later and were all thought to be associated with the dextrocardia (Schnitker, 1940), but eight weeks after admission the T waves were positive in all leads (Fig. 6B).

Depression of the T wave lasting some six weeks has not been previously described. It is unlikely to have been vagal or metabolic in origin; as it lasted too long. It may be analogous to that sometimes seen in acute nephritis, though T wave inversion in all three leads has not been reported in that disease. According to Goldzieher (1929), a large dose of adrenaline may produce myocardial lesions visible to the naked eye. Subepicardial hæmorrhages are recorded in autopsy findings after death in paroxysmal hypertension from pheochromocytoma. The long lasting T wave alterations seen in the present case were probably due to a small myocardial hæmorrhage, perhaps involving the conducting system.

DIFFERENTIAL DIAGNOSIS

The diagnosis rests on the history and the observation of an attack with paroxysmal hypertension and other phenomena. If spontaneous attacks are not seen, efforts should be made to induce one. Frequent readings of the blood pressure may detect symptomless paroxysms. The demonstration of excess adrenaline in the blood during or between crises is a specific test but is not always positive.

Intravenous injection of adrenaline may produce the same subjective feelings as an attack, but is not without danger. Estimation of serum potassium in the attack is suggested by McQuarry (quoted by Wells and Boman, 1937) since intravenous adrenaline may produce an 86 per cent rise in blood potassium figures. A very high value was found between attacks in the case recorded here. In deciding the site of the tumour, pyelography is much the most useful procedure. Perirenal pneumography is not recommended as it is hazardous and not very useful.

Paroxysmal hypertension occurs in a number of conditions. (1) *Pheochromocytoma.* (2) *Essential hypertension.* In this the blood pressure is always raised between the attacks, prodromes are common, the onset and end of the paroxysm are gradual, fits and cerebral eclipses are common, widespread symptoms are rare, and attacks are not precipitated by posture or pressure on the adrenals. Abnormal urinary findings and a leucocytosis are seen both in pheochromocytoma and in malignant hypertension. (3) *Symptomatic paroxysmal hypertension.* Recurrent attacks may occur in lead poisoning, eclampsia, tabes dorsalis, aortic reflux, angina pectoris, angina vasomotoria of Nothnagel, affections of the vagus, and thalamic tumour.

Where an attack has not been witnessed the history may be difficult to elucidate. Hyperthyroidism, diabetes mellitus, peptic ulcer, acute and chronic nephritis, malignant hypertension, surgical shock, polyarteritis nodosa, migraine, cerebral tumour, angina pectoris, cardiac neurosis, neurasthenia, and anxiety state may be simulated.

The vasovagal attacks described by Gowers (1907) and more recently by Ryle (1928) and Kinnier Wilson (1940) in some instances present a very close similarity to the attacks of the adrenal-sympathetic syndrome. Gowers considered that Nothnagel's syndrome was a closely allied phenomenon, and he pointed out that vasomotor spasm may attain a high degree in vasovagal attacks, being evidenced by coldness and pallor of the limbs and diminution of the pulse. Nothnagel's syndrome (see Lewis, 1931) is apparently identical in symptomatology with the adrenal-sympathetic syndrome. It is possible that some of Gowers' cases (e.g. his Case 1) and some of Nothnagel's were due to pheochromocytoma.

Treatment

The treatment of pheochromocytoma is to remove it. Laparotomy should be considered without undue delay as the benefits of successful removal of a pheochromocytoma outweigh the dangers of an operation in a case of secondary paroxysmal hypertension. Palliative treatment by sedatives or X-rays gives only transient relief.

Treatment of the paroxysm. Bleeding is most important. Morphine may be very valuable. Lumbar puncture will lower the blood pressure and relieve the headache in other types of paroxysmal hypertension, and should be useful in this one, especially for the headache which is severe and intractable. Vasodilators may give temporary relief, but worse discomfort later. For collapse following a paroxysm, adrenaline is specific (in contrast to its effect in surgical shock).

Pre- and post-operative measures. These are reviewed by Biskind *et al.* (1941). Chloroform, cyclopropane, and spinal anæsthesia should be avoided. The abdominal approach is recommended by most recent authors. Where the site of the tumour is uncertain, a laparatomy to locate the tumour and to establish the presence of the opposite adrenal body, with a later removal of the tumour by the lumbar route adds the real risk of a second operation but makes the actual excision a less disturbing procedure. This is important as operation may be accompanied by severe paroxysms. Incision of a large cyst may prevent these (Strombeck and Hedberg, 1939).

Operation was followed by severe shock in 17 of the 37 cases recorded. This shock is best combated by giving a dilute solution of adrenaline intravenously as described in the case report above. Where the blood pressure fails to respond to adrenaline, blood transfusion should be given. Salt and adrenal cortical hormone 10 c.c. should be given after operation.

Results of operation. In their excellent analysis of cases submitted to operation, Biskind, Meyer, and Beadner (1941) report 29 cases. The list is not quite complete: 3 cases (Belt and Powell, 1934; Volhard, 1931; Hatieganu *et al.*, 1939) which died after operation are excluded on inadequate grounds; 2 cases are omitted; one successful (Ody and Piotrowsky, 1933) and one fatal from post-operative shock (Keyser and Walters, 1924); and 3 successful operations have been recorded since (Brunschwig and Humphreys, 1940; Hamilton, 1940; and the present case).

If these cases are added, we get a total of 37 operations with 10 deaths. Of these 10 deaths after operation, 7 occurred in 19 cases reported to the end of 1936, and 3 in 18 cases reported since then.

Of the 27 survivors, 24 are probably quite well. In one case a recurrence of symptoms after operation responded to X-ray treatment (Borras and Meyer Mota, 1938).

Discussion

The cause of the paroxysm or vascular crisis is a sudden hyperadrenalinæmia of obscure origin which causes a widespread vasoconstriction and also increases the output of the heart. The sharp rise of blood pressure acting through the " depressor " reflex leads to a vagal discharge, which explains why the symptom picture includes not only adrenalinergic mechanisms but also cholinergic ones such as salivation.

A rise of blood pressure without symptoms is probably common. Attacks with symptoms but no rise of blood pressure are mentioned by Labbé, Tinel, and Doumer (1922) and by Bernal (1933). These may occur but it is certain that in most of the paroxysms with only localized symptoms, it is the symptoms and not the vasoconstriction that are localized. This is shown by the rise in systemic blood pressure. The local symptoms are secondary to the rise of blood pressure; abdominal pain probably being due to distension of vessels, angina pectoris to oxygen deficiency in the overworking heart muscle, and so on.

Specific localization of symptoms is seen in other types of paroxysmal hypertension; abdominal in plumbism, cerebral in eclampsia, anginal in aortitis, but each of these is not invariable, e.g. eclamptics may complain of abdominal pain with their paroxysms.

A very striking symptom is the feeling of prostration, which may last for half an hour after an attack consisting of a few seconds' palpitation or dizziness. Freeman *et al.* (1941) and others have shown that on stopping adrenaline infusion in dogs, shock with oligæmia develops. Large doses of adrenaline may be followed by prolonged vagal effect (MacDowell, 1931). According to Goldzieher (1929, p. 81) pheochrome overfunction may lead to complete exhaustion with morphological findings as in muscular overexhaustion.

Adrenaline in large doses diminishes muscle and somatic reflexes by a direct depressant action on the spinal cord (Schweitzer and Wright, quoted by Wright, 1942). This seems a likely explanation of the prostration, which is probably directly analogous to the " nervous exhaustion " felt after intense excitement.

The cause of the persistent hypertension sometimes seen with pheochromocytoma remains obscure. In continuous infusion of adrenaline, the blood pressure after an initial rise returns to normal (Freeman *et al.*, 1941). Strombeck and Hedberg (1939) in their case found the blood adrenaline between attacks was 30 times normal without persistent hypertension. But it is possible that in other cases there is a breakdown of the normal adrenaline destruction mechanism (see Richter, 1940) or there may be a dislocation of the normal mechanisms for regulating blood pressure. The common finding of albumen and casts in the urine after attacks suggests that renal damage sustained during paroxysms may be the cause, but this is doubtful. In some cases of pheochromocytoma with persistent high blood pressure, the kidneys at autopsy have been intact; in others after removal of the tumour the blood pressure has returned to normal, and in others it has returned to normal or below without operation.

On the other hand, it is possible that the vascular crises seen in essential hypertension, aortic valvular disease, tabes, eclampsia, and lead-poisoning, which may so closely resemble those of the adrenal-sympathetic syndrome, are themselves due to sudden discharge of adrenaline. Brandt and Katz (1933) reported that during hypertensive crises the blood has adrenalinic characters on biological testing, which are absent between the crises. Bernal (1933) obtained a rise of blood pressure by perfusing blood taken from a patient with essential hypertension during a crisis, and also with blood taken from a patient during a bout of lead colic. These are experiments that should be repeated; especially as bleeding is the treatment for any hypertensive paroxysm.

Summary

Two cases of adrenal-sympathetic syndrome due to pheochromocytoma (chromaffin tissue tumour of the adrenal medulla), are described.

The first is unusual in that though he had minor attacks almost daily for four years, there was only one major attack, which led to a diagnosis and operation, with cessation of the attacks.

The syndrome of chromaffin tissue tumours is reviewed. It is noted that while many cases show widespread symptoms, others show only local symptoms, though the vasoconstriction is generalized. Paroxysmal hypertension is the one sign common to all attacks. The treatment is removal of the tumour.

The close similarity between the hypertensive paroxysms of pheochromocytoma and those seen in other conditions, notably in essential hypertension, suggests that some at least of these other paroxysmal hypertensions are due to sudden discharge of adrenaline.

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RECIPROCAL BEATING INITIATED BY VENTRICULAR PREMATURE SYSTOLES

BY

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Reciprocal rhythm is a rare phenomenon. All reported cases with but one exception are instances of nodal rhythm with re-entry of the retrograde nodal impulse (1–3, 5–10, 12, 15, & 21–24). However, Wolferth and McMillan (1939) have described a case of sinus rhythm with re-entry of the antegrade sinus impulse. In the present communication a unique case is reported in which the reciprocal rhythm was initiated by ventricular premature systoles. So far as we are aware, this has not been described before in a human heart although it has been produced in the experimental animal (14, 17, & 19). The patient manifesting this arrhythmia was a 56 year old white woman (a private patient of Dr. D. C. Straus) who presented no evidence of organic heart disease and was sent up for analysis of her pulse irregularity. In Fig. 1 is shown her first cardiogram and in Fig. 2 records taken during and after left carotid sinus pressure and after exercise.

Fig. 1 shows a group of four ventricular beats which repeat themselves throughout, except at the end of lead III. The four QRS complexes in each group will be called R_d, R_e, R_f, and R_g respectively, and the three P waves, P_a, P_b, and P_c respectively.

It will be seen that P_a and P_b precede R_d and R_e and that the P_a–R_d and P_b–R_e intervals are constant in each lead and measure 0·14 sec. in lead II (0·08 sec. when measured from the peak of P to QRS onset). Further, the P_a–P_b intervals vary slightly; in lead I from 0·92–0·94 sec., in lead II from 0·90–0·94 sec., in lead III from 0·86–0·90 sec., and in the chest leads from 0·90–0·92 sec. The mechanism for the first two beats of the groups of four is therefore a sinus arrhythmia varying in rate from 64 to 70 beats per minute.

The third ventricular beat, R_f, is obviously a premature ventricular systole since it is premature, is not preceded by a P wave, and is prolonged and bizarre compared to R_d and R_e.

The fourth ventricular beat, R_g, is preceded by a P wave, P_c, in every instance, and it resembles R_d and R_e closely. Three types of P_c are seen:

(*a*) one that resembles P_a and P_b making allowances for the fact that P_c occurs superimposed on the S–T–T complex of R_f, viz. the second P_c in (C), the third P_c in (D), and probably all the P_c waves in (A);

(*b*) one that is strikingly different from P_a and P_b. This is best seen in leads II and III where it is sharply inverted while P_a and P_b are upright, viz. the second P_c in (B) and the first P_c in (D);

and (*c*) one that is intermediate in contour between (*a*) and (*b*), viz. the first and third P_c in (B), the first and third P_c in (C), and the second and fourth P_c in (D).

All three types of P_c are characterized by a tendency towards prematurity, viz. P_b–P_c is shorter than P_a–P_b. The P_c–R_g interval and the R_f–P_c intervals are not easily measured because the beginning of P_c cannot be located exactly. However, by comparing the intervals

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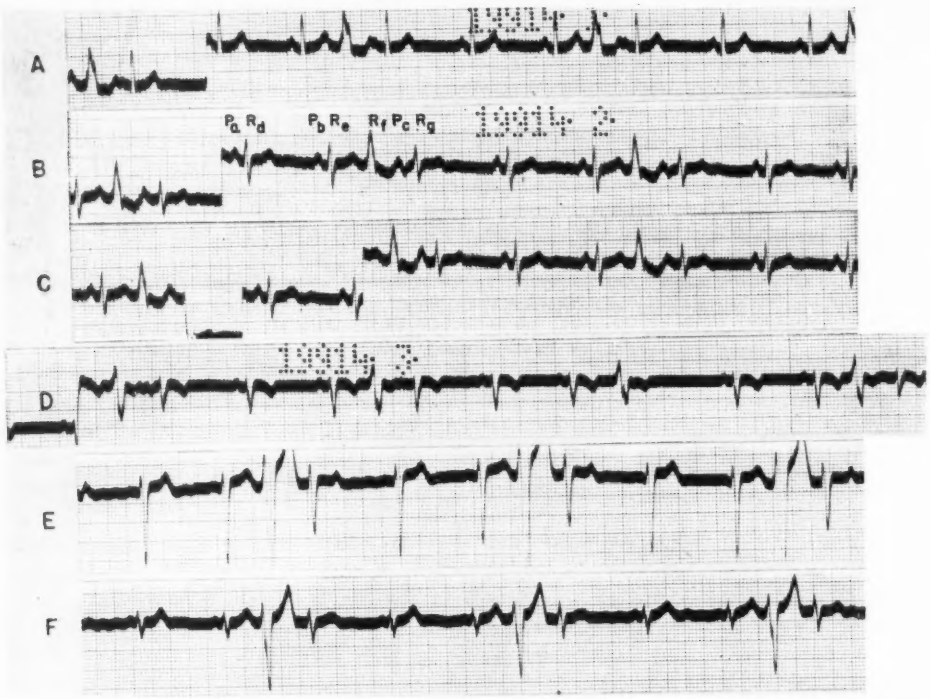

FIG. 1.—Electrocardiogram from the patient at his first visit. (A) is lead I; (B) and (C) are a continuous strip of lead II, the last beat of (B) being repeated as the first beat of (C). In (B) a group P_a, R_d, P_b, R_e, R_f, P_c, R_g is labelled. Discussed in text. (D), (E), and (F) are respectively leads III, CF_2, and CF_4. Note that P_c in the chest leads (E and F) is difficult to make out.

measured from the peak of P_c with similar measurements made from the peak of P_a and P_b, it is apparent that P_c–R_g (0·08–0·16 sec.) is equal to or longer than P_a–P_d and P_b–R_e. The R_f–R_g interval is constant for each lead, regardless of the position and contour of the intervening P_c. In leads I and the chest leads it equals 0·50 sec. and in leads II and III, 0·52 sec. Likewise such measurements show that R_f–P_c is equal to about 0·28–0·44 sec.; in those instances where P_c is inverted R_f–P_c is constant and measures 0·44 sec., and the same value is obtained in the third P_c in lead II where P_c is intermediate in contour between P_a and the inverted P_c; in all other instances R_f–P_c is shorter than 0·44 sec. and the contour of P_c varies.

On one occasion in lead III, P_c is not followed by R_g. In this latter instance P_c resembles P_a and P_b, and R_f–P_c is equal to 0·28 sec. R_f occurred later than usual in this instance, viz. R_e–R_f here equals 0·52 sec. as compared with the usual value of 0·41–0·44 sec. in the limb leads and 0·48 sec. in the chest leads.

At first sight the beat P_cR_g might be considered an auricular premature systole when P_c is abnormal, and a sinus beat when P_c resembles P_a and P_b. In the former case, we would be dealing with a pair of premature systoles, the first, R_f, a ventricular, and the second, P_cR_g, an auricular. In the latter case, we would be dealing with an interpolated ventricular premature systole, R_f. However, closer examination of the record and its measurements, together with the data obtained in the later records (see below) are opposed to this interpretation. The argument for the alternative interpretation we adopted is along the following lines.

The bizarre P_c waves resemble in contour retrograde P waves which are usually small and upright in lead I and sharply inverted in leads II and III. They are therefore considered

retrograde P waves. Such retrograde P waves could be due either (*a*) to retrograde conduction of the impulse from the ventricular premature systole R_f or (*b*) to retrograde conduction of an impulse arising in the A-V node which gives rise to R_g. Since a nodal premature systole, as assumed in (*b*) which shows fixed coupling with the preceding QRS, is most likely due to re-entry, the alternative explanations for the retrograde P waves become identical.

The acceptance of the view that the bizarre P waves are retrograde in origin permits consideration of the P_c intermediate between the bizarre ones and those resembling the sinus P waves. The intermediate P_c waves can be considered to be due to simultaneous invasion of the auricles from the sinus node and by the retrograde impulse. A comparable phenomenon seen in the transition from sinus to A-V nodal rhythm has led to the description of such beats as transitional complexes (Lewis, 1925), or fusion beats (Katz, 1941). The alternative explanation for the variable P_c contour would be to ignore the retrograde contour and conceive the P_c complexes as being auricular premature systoles from varying foci. The latter explanation is not as tenable as the fusion P assumption since it ignores the constancy of R_f–R_g regardless of the P_c contour and would not explain the occurrence of a P_c–R_g interval of less than 0·12 sec. in a subsequent record (Fig. 2 A).

FIG. 2.—Electrocardiograms (lead II) taken one month after that shown in Fig. 1. (A) is a record at rest and shows two instances where P_c–R_g is less than 0·12 sec. (B) is a record after exercise, and (C) during left carotid sinus pressure. They show that R_f–R_g (second pair in each strip) is longer than the R_f–R_g interval obtained in records at this time. (D) is also taken during left carotid sinus pressure. R_f–R_g in this strip, as in the first pair of (B) and (C) and both pairs in (A) show the usual duration found at this time. (E) taken immediately after left carotid sinus pressure shows one R_f.P_c combination not followed by R_g. The P_c in this instance is clearly of sinus origin. Discussed in text.

If the view that P_c waves differing from P_a and P_b in contour are associated with retrograde conduction, then the R_g that follows such a P_c cannot be of sinus node origin, since the sinus node impulse either does not invade the auricles or at least does not reach the A-V junctional tissues. R_g must therefore be due to the retrograde impulse responsible for P_c and hence is part of a reciprocal rhythm initiated by the premature ventricular systole R_f.

There remains the group of P_c waves which are almost identical with P_a and P_b. Two alternatives exist for R_g following such P waves. In fact both might be operative on different occasions. The simpler explanation would be to assume that R_g is of sinus node origin. In favour of this view is the fact that in subsequent records there were three occasions on which R_f–R_g, otherwise remarkably constant, was prolonged compared to the other R_f–R_g intervals and associated with a P_c–P_g longer than the usual sinus P–R, as might be expected after an interpolated ventricular premature systole (e.g. the second group in Fig. 2 B and Fig. 2 C). In

these three instances R_g is most likely of sinus origin. The remarkable constancy, with the three exceptions noted, of the R_f-R_g interval (regardless of the position and contour of P_c) favours the idea that R_g is part of a reciprocal rhythm. This reciprocal rhythm is initiated by R_f and re-entry to the ventricles of the retrograde impulse occurs at a point below the auricles somewhere in the A-V junctional tissues above the bifurcation of the common A-V bundle at a time before the sinus impulse reaches the re-entry point.

Several other facts became apparent in the series of records (of lead II only) taken a month after Fig. 1 which support our explanation. These were recorded during rest, after exercise, during and after left carotid sinus pressure, and during the first 45 minutes of the action of atropine sulphate (1/75 grain intramuscularly) (Fig. 2).

(1) In these records a total of 91 R_f complexes were encountered, the P_c that followed was of sinus contour in 87, retrograde in none, and suggested a fusion P in 4. In 38 instances a combination $R_fP_cR_g$ occurred.

(2) There was a sinus arrhythmia present with slight variations of P contour indicating a wandering pacemaker, but the P_c contour (even allowing for the distortion due to its superposition on the S–T–T of R_f) varied more than the sinus P waves.

(3) There was a shortening of the P–P_c interval and a lengthening of the P_c–P interval apparently due to the same mechanism as so-called ventriculo-phasic sinus arrhythmia in heart block.

(4) The occurrence of R_g depended on the R_f–P_c interval. R_f–P_c varied from less than 0·16 to 0·32 sec. when R_g was absent, and from 0·34 to 0·42 sec. when R_g followed. The variations in R_f–P_c were due to the sinus arrhythmia as well as to the occurrence of the premature ventricular systole, R_f, at different times after the sinus QRS, i.e. R_e–R_f varied from 0·36–0·56 sec.

(5) In all instances where P_c was not followed by R_g, P_b appeared to be of sinus origin.

(6) The interval R_f–R_g was remarkably constant, being 0·48 sec. In three instances it was longer, equalling 0·51, 0·52, 0·52 sec. (Fig. 2 B & C). In these three, P_c occurred relatively early (at the shortest R_f–P_c distance followed by an R_g), resembled the sinus P, and was associated with a prolonged P_c–R_g interval (0·15, 0·18, 0·18 sec. respectively) as compared with other P_c–R_g intervals (0·06–0·14 sec.). These facts confirmed the view that R_fR_g represent reciprocal rhythm except when the R_f–R_g interval is definitely prolonged; in the latter case, R_g is considered to be of sinus origin. This has already been referred to above.

(7) The occurrence of P_c–R_g of less than 0·12 sec. was encountered three times (Fig. 2 A), indicating that R_g in these instances can not be of sinus origin, nor due to any impulse spreading from the auricles to the ventricles after the inscription of P_c, a matter already referred to above. In determining the position of P in this and other instances, a task not always easy, we made use of the duration of electrical systole of R_f in other beats in the record.

The mechanism which we believe underlies this arrhythmia can best be summarized diagrammatically as in Fig. 3. A sinus rhythm is present throughout and in addition there are ventricular premature systoles; these two pacemakers determine the arrhythmia. The ventricular premature beats have retrograde conduction and the contour of P_c following them will depend upon where the retrograde impulse and sinus impulse meet and interfere with each other. This is determined by the relative time of discharge of the sinus and ventricular pacemakers and by the retrograde conduction time. The possibilities are:

(a) near the sinus node (Fig. 3 A) in which case the auricles will be controlled by the retrograde impulse and P will have the retrograde P contour;

(b) near or within the A-V junctional tissue (Fig. 3, C, D, and E) in which case the auricles will be controlled by the sinus impulse and P will be of sinus P contour; or

(c) somewhere in the auricles (Fig. 3 B) in which case the auricles will be controlled in part by the sinus and in part by the retrograde impulse and P will have a contour intermediate between the sinus and retrograde P, i.e. it will be a fusion P.

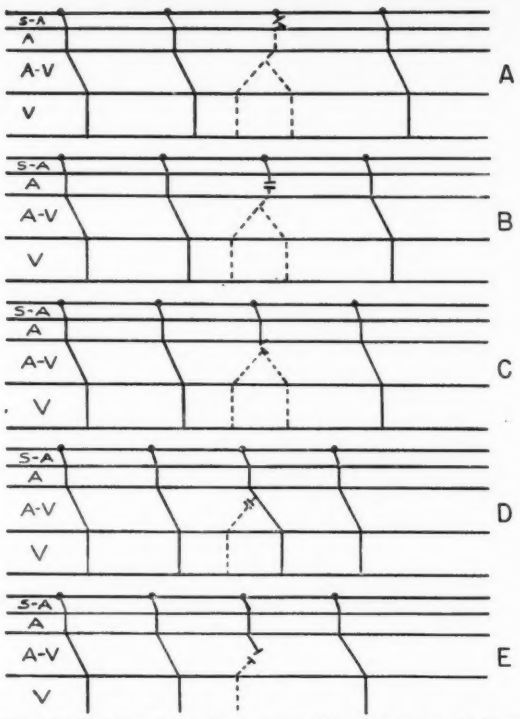

FIG. 3.—A series of diagrams illustrating the various circumstances encountered in this patient, showing the various locations of interference between the sinus and retrograde impulses as well as the conditions under which re-entry and reciprocal rhythm are established. Discussed in text. Dotted lines represent the ventricular premature systole, the retrograde conduction, and the re-entry leading to reciprocal rhythm. S-A, A, A-V, and V represent conduction respectively within the sinus node, auricles, A-V junction, and ventricles.

The retrograde impulse in travelling through the A-V junctional tissue finds a point at which it can become antegrade again and re-enter the ventricles. The fact, pointed out above, that the interval R_f–R_g is fixed except on three occasions begs coincidence too much and suggests that in all but the three exceptions the combination of the premature ventricular systole and the ventricular beat that follows are instances of reciprocal rhythm. Since this occurs at times when the auricles are under the control of the sinus node and not invaded by the retrograde impulse from the premature ventricular systole, and at other times when P_c suggests a fusion P, with a P_c–R_g interval of less than 0·12 sec., it follows that re-entry takes place below the auricles in these cases, and therefore presumably this is the location of re-entry in all cases where reciprocal rhythm occurs. Further the fact that the second ventricular complex of the reciprocal rhythm resembles those of sinus origin indicates that the re-entry point is above the bifurcation of the common bundle. It is our inclination to believe that it is somewhere in the A-V node where branching is more prevalent than in the A-V bundle. The conditions for re-entry have been clearly analysed by Schmitt and Erlanger (1928) as a monodromic condition in some fibers with a heterodromic condition in adjacent fibers. In other words different degrees of unidirectional block in adjacent fibres predispose to re-entry of the impulse. In our case the retrograde conduction time (R–P) of about 0·40 sec. in those instances where P_c is retrograde (Fig. 1), as compared to a P–R of 0·14 sec. of the sinus beats proves that retrograde conduction is markedly delayed.

We are now prepared to consider what happens in the A-V junctional tissue in those beats

in which the sinus impulse invades it after the premature ventricular systole is initiated. Two main possibilities exist.

The sinus impulse can meet the retrograde impulse before the latter has passed the point of re-entry, and so prevent not only the retrograde impulse from entering the auricles but also the establishment of the reciprocal rhythm. If the sinus impulse enters sufficiently early it itself will be prevented from entering the ventricles and the ordinary variety of premature ventricular systole with a fully compensatory pause will ensue (Fig. 3 E). If, however, the sinus impulse enters later so as to reach the point of re-entry just ahead of the retrograde impulse, it may find the tissue through which the retrograde impulse usually re-enters in a state permitting its passage into the ventricles. Here, then, the re-entry would be prevented but a second ventricular complex would follow the premature ventricular systole at an interval somewhat longer than that between the ventricular beats of reciprocal rhythm, because of prolongation of the conduction through the A-V junction resulting from the fact that the sinus impulse travels through earlier than the re-entry impulse (Fig. 3 D). This then would be an example of an ordinary interpolated ventricular premature systole.

The sinus impulse can meet the retrograde impulse after the latter has passed the point of re-entry. In this case, the sinus impulse would prevent the retrograde impulse entering the auricles, and the retrograde impulse would prevent the sinus impulse from reaching the ventricles. However, since re-entry had occurred, the retrograde impulse would actually cause the following ventricular beat. In short, the post-extrasystolic beat would have a sinus P wave and a ventricular complex due to re-entry of the retrograde impulse of the preceding premature ventricular systole, the P and QRS thus being unrelated (Fig. 3 C). In these cases the R–R interval between the two beats of the reciprocal rhythm would be expected to have the same duration as in those cases in which a retrograde P can be shown to occur between them; and this was actually true.

The occurrence of re-entry before the impulse reaches the auricles, found in our case, may be found in any case of reciprocal rhythm, as Drury (1924) suggested and as has been postulated by Scherf and Shookhoff (1926) and by Cutts (1937). The case of Gravier *et al.* (1939) showing reciprocal rhythm and varying P wave contour could be explained, in like manner, by assuming re-entry below the auricles with interference between the retrograde and sinus impulses above the level of re-entry. Obviously, the " sandwiching " of the P wave between two ventricular complexes (White, 1915) does not constitute an integral part of reciprocal rhythm. Even when such a P wave is retrograde in character it indicates merely retrograde conduction, a condition necessary for re-entry.

The significance of a sinus P between a pair of ventricular beats in a case like ours may be evaluated by the duration of the P–R interval compared with the P–R of the sinus beats. When the P–R is equal to or shorter than the sinus P–R, the second beat would be considered a reciprocal beat, provided the R–R interval equalled that of known reciprocal beats. When the P–R is longer than the sinus P–R duration and the R–R interval is also prolonged while P resembles the sinus P waves, then, the second beat would be considered a sinus beat. The fortuitous combination of a sinus P wave between two ventricular beats indicates " pseudo-reciprocal rhythm " (Katz and Kaplan, 1938).

The case reported by us suggests that even in the absence of retrograde conduction in the form of retrograde P waves, re-entry may be responsible for other instances of fixed coupling, whether this occurs as in our case between two premature systoles or between a premature systole and the preceding sinus beat. This possibility though previously considered (Mines, 1913; de Boer, 1921; and Lewis, 1925) has been questioned by others (Scherf, 1930, and Rothberger, 1931). Our case is important since it definitely favours the re-entry mechanism. When the second ventricular complex is bizarre compared with the sinus beats the re-entry may be below the bifurcation of the common bundle, and this variety is the common one encountered. Probably other instances like ours will be discovered.

Summary and Conclusions

A case is presented showing sinus rhythm and ventricular premature systoles followed at a fixed interval by another premature ventricular complex of supraventricular origin. The occasional presence of inverted P waves between the two premature ventricular beats suggested reciprocal rhythm. This was substantiated not only by the constant interval between the two premature ventricular beats but also by the occurrence of P waves preceding the second premature ventricular beat at a distance so short as to preclude the possibility of conduction of an impulse from the auricles to the ventricles in the second beat.

In our case evidence is presented to suggest that the point of re-entry was below the auricles and above the bifurcation of the common bundle, presumably within the A-V node.

It is pointed out that the retrograde P waves in cases of reciprocal rhythm due to re-entry of retrograde impulses merely indicate the presence of retrograde conduction, without in themselves constituting an essential part of the mechanism underlying reciprocal rhythm.

The various possibilities of interference, in our case, between the sinus impulse and retrograde impulses causing reciprocal rhythm are evaluated and instances of each cited.

Our case indicates that instances of fixed coupling of premature ventricular beats even in the absence of P waves, indicative of retrograde conduction, may be examples of re-entry.

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HEART FAILURE IN THE AGED

BY

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Heart failure in old age differs in many ways from that in earlier life. Aetiology, pathology, course, symptoms, and treatment are all modified by the special circumstances. For example, rheumatic disease and syphilitic disease are not common over the age of sixty; but toxæmia, especially after pneumonia, becomes an important factor. Before middle age, the pathological state of the heart itself is all important: after this, the condition of the peripheral vessels also must be taken into account. In the young, recovery is more rapid and lasting: in the old, relapses are the rule and not the exception. Congestive failure with " back pressure " is the chief form of failure in early life: but ischæmic failure, as angina pectoris and coronary thrombosis, becomes more frequent as old age approaches. The present paper is an analysis of the history of cardiac failure in seventy-five old or elderly persons, and attempts to point out the special characteristics arising in senility. Owing to lack of post-mortem facilities in war time, only the clinical features are available for consideration.

Aetiology

The series was composed of 75 patients whose ages ranged from sixty-two to ninety-two. All were males and all but five were Chelsea pensioners. No congenital or rheumatic heart disease was found, and the youngest patient was the only one with syphilitic heart disease. The commonest cause of cardiac failure was a high blood pressure, which was the sole factor, apart from arteriosclerosis, in 27 cases. Coronary arterial disease alone accounted for 13, while coronary disease and hypertension were found together in 4 cases. A toxic myocardium, resulting from pneumonia or some other infection, was the cause of failure in 11 cases, 2 of them having had hypertension previously and 2 others having had previous coronary thrombosis. The remainder were originally classed as " myocardial degeneration," but more careful study of their records enabled them to be analyzed more precisely. Six of these were probably due to past high blood pressure. Each had the heart enlarged to the left, and was admitted to hospital with a blood pressure that continued to fall until death. Two more followed long standing asthma and chronic bronchitis, so were classified as chronic cor pulmonale. One was a heart block of unknown cause. One showed increasing peripheral ischæmia with a blood pressure that fell steadily until death. All the rest showed congestive heart failure, complained of dyspnœa on exertion, had no raised blood pressure, and never had pain in the chest or arm on effort; this, or course, may have been because they never exerted themselves enough. These results are summarized in Table I.

TABLE I

Aetiology of Heart Failure in the Old

Hypertension alone (including 6 where the diagnosis was " probable past hypertension ") ..	33
Coronary disease (alone 13, and with hypertension 4)	17
Myocardial toxæmia	11
Various (chronic cor pulmonale 2, heart block (? cause) 1, syphilitic heart disease 1, and uncertain, 10)	14
	75

Varieties of Failure

While congestive failure, anginal failure, and coronary thrombosis are among the commoner forms of cardiac defeat, other varieties peculiar to senility also occur. These seem to result from the inability of the left ventricle to propel the blood against the increased resistance of the thickened and narrowed peripheral arteries. The basic pathology shows itself as peripheral ischæmia, sometimes intermittent, sometimes constant, and sometimes progressive. Steiglitz (1935), in his book *Abnormal Arterial Tension*, refers to this conception as relative hypotension. The dominant symptoms are usually cerebral in origin. One symptom-complex of this type has already been described by the present writer (1941 and 1943) under the name of progressive cerebral ischæmia. Here, an arteriosclerotic patient with high blood pressure shows first mental confusion, then restlessness or violence, and finally becomes comatose while his systolic figure falls from its previous high grade to the ultimate level (around 100 mm.) at which death ensues in such cases. This syndrome may follow right or left heart failure which has been treated with apparent success, or may result from myocardial toxæmia after an infection, such as pneumonia. This latter occurrence was mentioned by a former physician to the Royal Hospital in 1863.

One other form of " forward " failure requires notice. This is the gradual but steadily increasing feebleness, accompanied by a slowly falling blood pressure, seen in a few patients. There is no angina pectoris, no congestive failure, no paroxysmal dyspnœa, nor are cerebral symptoms prominent. As the great Harvey says in Chapter 3 of *De Motu Cordis et Sanguinis*— " When this (left) ventricle contracts languidly, the pulse in the arteries is scarcely perceptible."

The varieties of heart failure are summarized in Table II.

TABLE II

Varieties of Failure in the Old

Left heart failure (paroxysmal dyspnœa)	16
Right heart failure (congestive)	13
Right and left heart failure together	9
Coronary thrombosis	10
Angina pectoris	4
Coronary ischæmia and right heart failure	3
Cardiac stoppage	3
Progressive cerebral ischæmia alone	12
Other forward failure	5
	75

Other cases, provisionally labelled as relative hypotension, have been excluded from the present series. This was on account of the difficulty in separating them clearly from what might be termed arteriosclerotic dementia. Such patients often die a non-cardiac death, e.g. from hypostatic pneumonia or enteritis. In practice, hypostatic pneumonia must be distinguished from pulmonary œdema of cardiac origin. The latter benefits from the administration of mersalyl as a rule: the former often seems to be made worse by it.

Discussion

The first point which appears from the consideration of the above facts and figures is the frequency of multiple ætiology, when compared with causes of heart failure in young persons. Arterial thickening probably played a part in most of the cases, usually in association with hypertension or disease of the coronary artery. Sometimes myocardial toxæmia was superadded on top of these causes, and this made a fatal prognosis almost inevitable. Secondly, no less than 13 per cent of the cases had heart failure of which the cause was uncertain, even after repeated clinical examination. Although the term " myocardial degeneration " is deservedly disliked by cardiologists, some label must be applied to those cases of congestive failure whose cause cannot be determined during life with any degree of certainty. Arterio

sclerosis can be considered as playing a part both as external resistance to the output of the left ventricle and also by lessening the nutrition of the myocardium. Yet cases are often met, with thickened and tortuous arteries, who do not complain of any discomfort in chest or arm on normal exertion. This absence of symptoms of angina pectoris has been remarked by previous medical officers at the Royal Hospital (Lipscombe, 1932). Out of the four patients in the series, one was a private case and one followed coronary thrombosis; while the time taken to collect the total of seventy-five was over four years.

As noted above, high blood pressure is the commonest cause of heart failure in the series. This is as one would expect, since between forty and fifty per cent of Chelsea pensioners show a systolic pressure above 160 mm. Such cases die in congestive failure (52 per cent), from myocardial toxæmia (11 per cent), with progressive cerebral ischæmia (33 per cent), or with a gradually falling blood pressure (4 per cent). In the patients with congestive failure, the right ventricle was affected as often as the left, which suggested that the hypertension was not the only factor to be considered.

The final impression remaining was that the level of the blood pressure and the state of the arteries were the two deciding factors in prognosis. Once the former was unable to overcome the resistance of the latter, ischæmia of vital organs was present. Clinically, this usually showed itself by increased restlessness and a desire to get in and out of bed repeatedly without reason. When this occurred, a fatal termination was not far off.

Summary

The causes and forms of heart failure in 75 old persons are described.

The commonest causes of failure were high blood pressure, disease of the coronary artery, and myocardial toxæmia.

In 13 per cent of the cases, the cause of heart failure remained uncertain after repeated clinical examination.

The occurrence of " forward " heart failure, with peripheral ischæmia is described; and the importance of arteriosclerosis in producing circulatory failure is stressed.

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A CASE OF MYXOMA OF THE LEFT AURICLE

BY

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In their paper on this subject Fawcett and Ward (1939) remark that only rarely do descriptions of this interesting lesion appear in British publications, there being only one report in the nine years preceding their article. The condition is well reviewed in their paper and in that of Gilchrist and Millar (1936). It is the purpose of this article to describe a further case with an autopsy report.

Description of the Case

The patient, a woman of 33 years of age, was admitted to hospital with severe cardiac failure. There was a story of " growing pains " at the age of 17, but no history of rheumatic fever or of chorea. The family history was of no significance.

Her earliest complaint, which was of shortness of breath on exertion, started a year before admission; there was also a two-months' story of palpitation and swelling of the feet in the evenings. She managed to continue her work about the house until five weeks before admission, when on her doctor's advice she retired to bed. All these symptoms continued with the addition of a productive cough, loss of appetite, thirst, a feeling of " fullness and wind " in the abdomen, and great discomfort when lying flat in bed, this necessitating her being propped up on pillows.

On examination she was dyspnœic and cyanosed with an obvious malar flush. The neck veins were greatly distended but were not pulsating. There was no clubbing of the fingers. There was a mild degree of œdema of the legs, sacrum, and back, up to the rib margins. A large smooth tender liver could be palpated three fingers below the right costal margin; there was no demonstrable pulsation. No splenic enlargement could be made out, examination being hindered by a well-marked ascites. The pulse was very feeble, its rate being approximately 130 a minute with bouts of irregularity due to extrasystoles. There was no palpable thickening of the radial arteries and the blood pressure was 120/80. To percussion the heart was enlarged both to the right and to the left. The cardiac impulse was forceful and diffuse, in marked contrast to the quiet pulse. There was a systolic murmur, maximal at the apex and radiating diffusely, a loud pulmonary second sound, and then a mid-diastolic

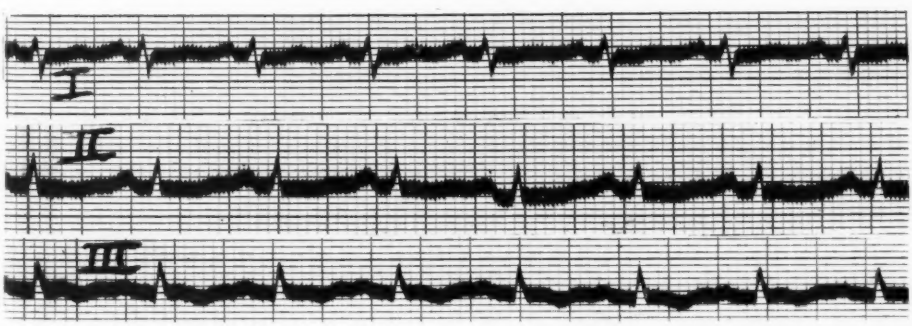

FIG. 1.—Electrocardiogram showing general low voltage response ; none of the extrasystoles that were noted clinically are seen in this record.

" filling type " murmur heard best internal to the apex. The bases of both lungs were dull to percussion, and crepitations were generalized but most marked at the bases posteriorly.

On these findings a diagnosis of mitral stenosis and heart failure was made. There was no response to digitalis and diuretin, and mersalyl failed to bring about a diuresis, the œdema steadily increasing. Terminally she developed coupling and tripling of the beats and digitalis was withdrawn. During her stay she was very drowsy. A cardiogram showed general low voltage (Fig. 1); no radiological examination was possible.

On the evening of the fourth day she suddenly had an attack of intense dyspnœa and began coughing up a considerable amount of clear frothy fluid. Death occurred in about five minutes.

Pathological Report (Abstract)

The body was of a well-developed and fairly well-nourished subject; there was œdema of the lower extremities. The pericardial cavity was enormously enlarged, measuring 22 cm. from apex to base, 15 cm. transversely, and 12 cm. antero-posteriorly. It contained about 150 c.c. of clear fluid. The heart was enlarged, especially on the right side, and the apex was formed by the greatly enlarged right ventricle. The right auricle was distended by 84 g. of post-mortem clot; no ante-mortem thrombi were present. The right ventricle was dilated and hypertrophied to a thickness of 0·8 cm. measured midway between the apex and the base. The dilated pulmonary ring measured 9 cm. The tricuspid and pulmonary cusps were normal. The left auricle was much dilated and largely filled by an enormous myxoma (Fig. 2). This

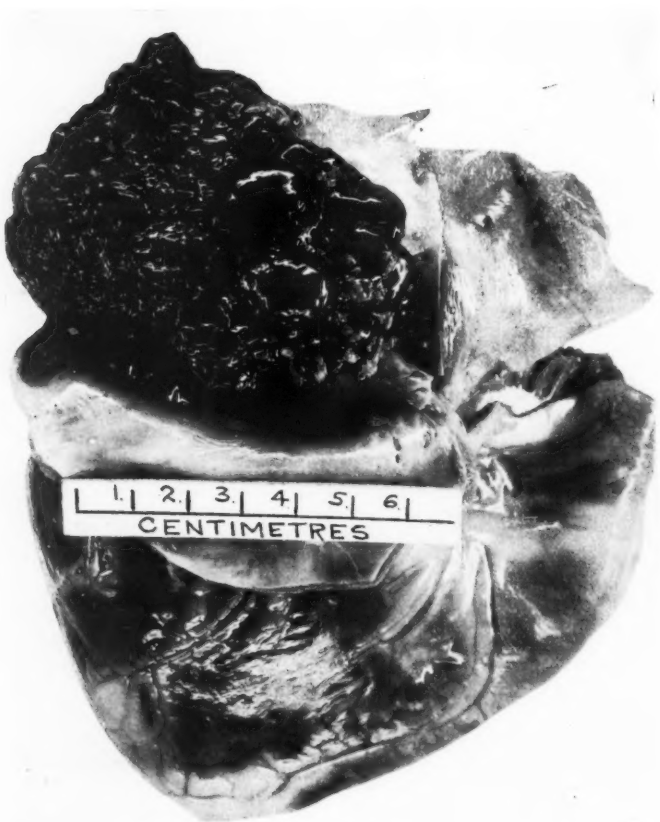

Fig. 2.—Photograph of the heart with the tumour in situ. The specimen is fresh and unfixed.

measured 7·5 cm. transversely, 5·9 cm. from above downwards, and was 5·5 cm. thick. It was adherent to the septal wall of the left auricle by a narrow pedicle 1 cm. in diameter. Although not actually touching it, this pedicle was attached just opposite the left edge of the foramen ovale. Except for a few small areas of white and red clot this tumour presented externally a very translucent surface partly smooth and partly rippled. There was no mitral stenosis, the valve admitting four fingers easily, and there were no ante-mortem thrombi in the auricle apart from those on the surface of the myxoma.

The myxoma had sufficient freedom to press against the left auricular wall opposite the mitral valve, where occlusion must have been very marked. Apart from this it practically filled the auricle, and only the auricular appendix and the actual mitral orifice were not filled by growth. The pulmonary veins must have been obstructed, and only one, the left inferior, seemed to have escaped obstruction by the myxoma.

The left ventricle, in contrast to the right, was short and atrophic. The heart and the myxoma weighed 450 g.

The lungs showed the induration of chronic venous congestion with an intense œdema and some recent infarcts; the right weighed 840 g., the left 650 g. The main pulmonary arteries showed slight dilatation but no atheroma. The liver had a well-marked nutmeg appearance. Other organs also showed signs of congestion and numerous infarcts of varying ages. The serous sacs contained a moderate amount of clear transudate.

Microscopically the tumour showed the appearances typical of myxoma, with long pro-

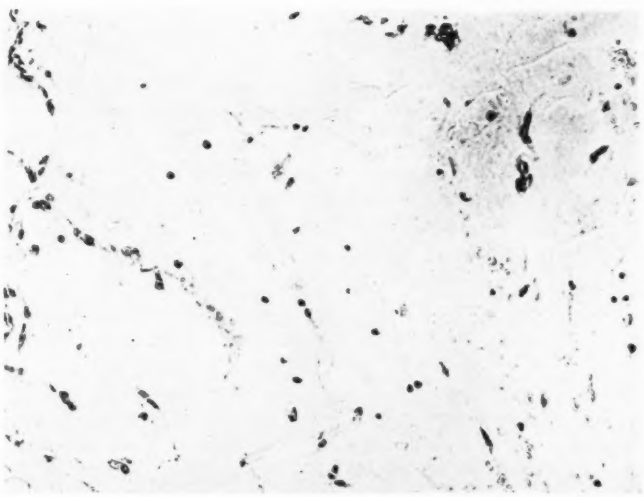

FIG. 3.—Microphotograph of a section of the tumour stained by Weigert's iron hæmatoxylin and van Gieson. Magnification ×180.

cessed myxoma cells rather widely scattered in a pale staining hyaline matrix; nuclear irregularities and mitoses were not seen. It was covered by a layer of endothelium, but here and there this was lacking, being replaced by thrombus (Fig. 3). Some of these areas contained a little hæmosiderin, but elsewhere, including all the deeper parts of the tumour, there was no pigment, fibrous tissue, or other indication of organized blood clot.

COMMENT

There have been a great many arguments as to whether these cases are true tumours or organized thrombi; the papers of Hamilton-Paterson and Castleden (1942), of Fawcett and Ward (1939), and of Yater (1931) summarize these discussions. There can be little doubt

that the mass in the auricle in the present case was a true myxoma. The naked eye and microscopical appearances were of myxoma, and there was no lesion such as mitral stenosis present to account for thrombosis. There was no evidence of rheumatic infection. Again it arose from the characteristic site—the margin of the foramen ovale—where myxomatous rests have been found (Ribbert, quoted by Fawcett and Ward). There was no deep siderosis or fibrosis which would suggest that the mass was an organized thrombus.

The tumour must have been of slow growth and long duration. The chronic venous congestion was as marked as in the average case of mitral stenosis, and as the patient had cardiac symptoms a year before death the tumour must then have been large enough to cause such symptoms and the chances are that it was not then much smaller than it was at death. The infarcts in the organs in the systemic circulation were considered the result of detachment of clot from the surface of the growth; most of them were recent.

Certain of the features of this case are of interest as having been found in records of other patients with this lesion. The case of Gilchrist and Millar died suddenly as did this one, and a similar mode of death has been not infrequent in previous reports. The mechanism in this case would appear to have been a settling down of the tumour in the mitral orifice, this giving rise to a picture like acute left ventricular failure with pulmonary œdema. Other cases have been reported as being liable to attacks of paroxysmal dyspnœa. Sudden death may occur in patients with or without a previous cardiac history (Yater, 1931).

No story of postural fainting attacks or of pain was elicited. It was not noted whether any alteration in the murmurs took place with change of posture. There was no response to treatment, this being in accordance with the usual reports.

The commonest clinical diagnosis is of mitral stenosis, for the condition of auricular myxoma is so rare that it is not likely to be considered, and the picture produced by the mass obstructing auricular blood flow is very similar, in this case no doubt producing the mid-diastolic murmur. Gilchrist and Millar remark ". . . occasions may arise in the presence of heart disease of unknown ætiology, particularly if symptoms be unusual and physical signs difficult to interpret, when the diagnosis might well come to mind, perhaps most readily by a process of exclusion."

Summary

A case of myxoma of the left auricle with congestive heart failure and sudden death is presented with an autopsy report.

My thanks are due to Dr. J. G. Thomson for his kindness in giving me the use of his autopsy report, and to Dr. J. C. Spence to whose ward the case was admitted.

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CIRCULATORY FAILURE DUE TO VITAMIN B DEFICIENCY

BY

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Cases of cardiac failure due to deficiency in vitamin B1 have been recognized in this country, and although the number of reported cases is small, their recognition is important since treatment by adequate doses of vitamin B1 is rapidly effective, whereas the usual methods of treatment fail. Most cases so far reported occurred in patients drinking too much alcohol and living on an inadequate diet, but a few were caused by deficient diet alone. Observations on three cases of " avitaminosis-B1 heart " showed some unusual features which seem to justify a communication. Two of the three drank too much alcohol, but in the remaining one the condition was caused solely by deficient diet.

Case Reports

Case 1. A man, aged 42, was referred to me on October 25, 1939, because of a dry irritative cough of two months' duration, the bouts of coughing being precipitated by exertion and often terminated by vomiting. Other complaints were general weakness, especially in the legs, and shortness of breath, even on walking slowly on the level. Latterly intermittent swellings had occurred in various parts, especially in the face, legs, and penis; such swellings developed rather quickly, in the course of a few hours, lasted for varying periods of time, and subsided again in the course of a few hours. He " had always drunk too much," chiefly port, cheap wine, and some beer; his appetite had steadily deteriorated: a small breakfast was his only solid meal and this he often vomited.

On examination, he had a hacking, brassy cough, reminiscent of the type met in cases of mediastinal tumour or aortic aneurysm. The face was puffy and pale, and the left mandibular region was diffusely swollen. The right lobe of the thyroid was slightly enlarged. There was a regular tachycardia of 98, a short systolic murmur over the apex, and a few fine crepitations over the right base. The blood pressure was 130/85. The lower border of the liver was just palpable on deep inspiration. On the right calf were three shallow ulcers. Radiologically the heart was much enlarged to the right and left; the normal concavity on the left border was absent and the region of the pulmonary conus was slightly prominent. Hæmoglobin, 70 per cent. There was no œdema of the legs or genital organs, but when seen one week later there was marked œdema of the penis, which according to the patient had come on in the course of a few hours; there was also slight œdema of the ankles. An electrocardiogram (Fig. 1A) showed sinus tachycardia, rate 98. The main deflections in all three limb leads were directed upwards and there was a small S I and a small Q III. The T waves in lead I and the left pectoral chest lead were very wide, shallow and upright and had a dome-like appearance with their convexity directed upwards, originating in the iso-electric line in lead I and slightly (1·5 mm) above it in the chest lead; there was no high take-off. T II was almost absent and T III inverted. The duration of the electrical systole (Q–T interval) was greatly increased. It is always related to the heart rate and using the formula most commonly employed: $Q\text{–}T = K \cdot \sqrt{\text{length of cycle}}$, K (calculated in lead I) was found to be 0·49 (upper limit of normal 0·43 according to Shipley and Hallaran, 1936); the duration of Q–T was also considerably outside the normal limits of the diagram worked out by Hegglin and Holzmann (1937) to show graphically the range of normal Q–T intervals with different heart rates.

The patient was put on vitamin B1 (Betaxan, 25 mg. by injection, daily for 4 days, and later once a week, in all 7 injections, also 20 mg. by mouth daily), and when seen again on November 15 his condition had improved. The swellings, cough, and crepitations had disappeared and the dyspnœa was considerably less. He had lost 17 lb. in three weeks. The heart shadow had decreased in size. Fig. 1B showed conspicuous changes as compared with Fig. 1A: R I had increased in height and the main deflections in lead III were now directed downwards and grossly slurred; T I had become inverted and T III upright, the R–T in lead I was curved, with the convexity directed upwards. The duration of the electrical systole had further increased, K being 0·50. Altogether the tracing showed features most commonly seen in cases of coronary disease. When seen again on December 8 the patient felt fit, and apart from the ulcers on his leg which had not quite healed, all his symptoms and

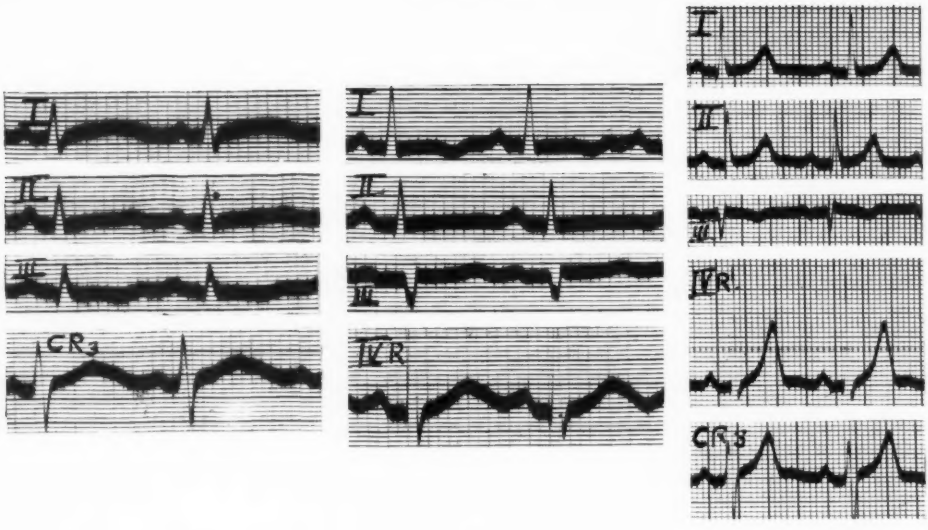


FIG. 1.—Case 1. (A) Oct. 25, 1939; (B) Nov. 15, 1939; (C) Aug. 23, 1940. Time markings in (A) and (B) 1/25 sec., in (C) 1/25 and 1/5 sec. In this and the subsequent figures: I, II, III, limb leads; IVR, right arm—apex; CR_3, right arm—fourth left intercostal space midway between left border of sternum and midclavicular line. For description of changes, see text.

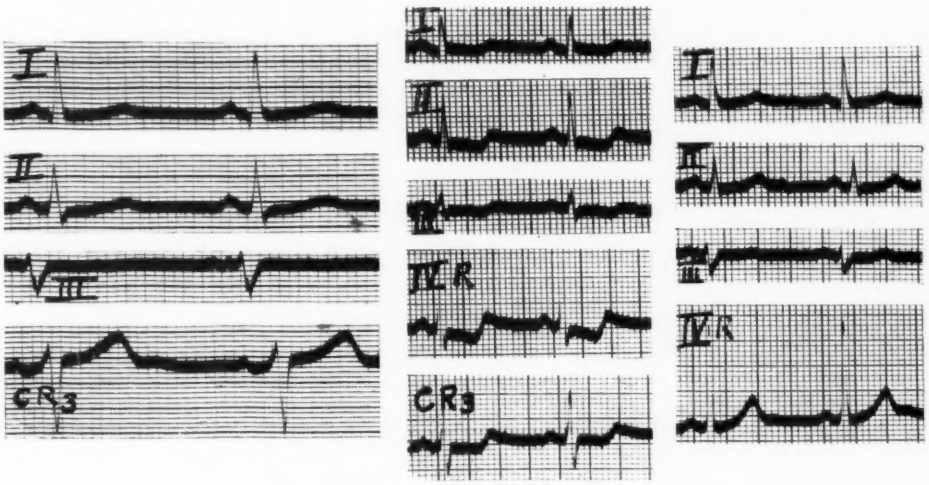
signs had disappeared. A cardiogram showed a rate of 92; R II had become higher and small R waves had appeared in lead III; T I and T II were upright and normal in shape, measuring 3 and 2·5 mm. respectively; T III had decreased in height to 0·5 mm. The chest lead (apical) was normal. The duration of the electrical systole had considerably decreased, K being 0·46. The patient felt well until March, 1940, when he started to drink again heavily. He discontinued vitamin B1 in June, 1940, but took halibut liver oil and malt, and when seen again in August, 1940, complained of a continuous feeling of anxiety and slight œdema of the ankles. A cardiogram (Fig. 1C) was normal in all leads, showing some left axis deviation; the rate had decreased to 71–77. The duration of the electrical systole had become normal, K being 0·42. Subsequently, the patient discontinued all treatment in spite of drinking even more heavily. When seen again in October, 1940, his general condition had deteriorated, with increased feeling of anxiety, morning sickness, some cough and occasional paræsthesiæ in the ankles, but swellings had not recurred and the cardiogram was unchanged.

Case 2. A man, aged 62 (in 1942), had been under periodical observation since 1922 for moderate emphysema of the lungs and atherosclerosis, which were very slowly progressing. Apart from slight dyspnœa on exertion, his condition did not give rise to any complaint. There was also a congenital neurological lesion diagnosed by a neurologist as forme fruste of Little's disease. Apart from very occasional dysphasia and ocular disturbances, he was free from complaints and the condition had remained stationary all his life. A cardiogram in 1937 (Fig. 2A) showed sinus rhythm, rate 64; there was left axis deviation with notching of S III. T I and T II were flat but upright, the S–T intervals in lead I were normal and in lead II slightly (<1 mm.) depressed below the iso-electric line; the chest lead (left pectoral) was normal. The main physical findings in 1939 were the signs of moderate emphysema of the lungs, a long systolic murmur over the apex, some rise in blood pressure (170/100) and bilateral extensor plantar reflexes.

The patient had always taken a fair amount of whisky, but while being on a full diet did not show any signs of alcoholism or vitamin deficiency. In the autumn of 1941, however, he increased his consumption of alcohol to an average of three-quarters of a bottle a day and lived almost exclusively on carbohydrates (Ovaltine and milk puddings). When seen on February 7, 1942, he was so weak that he was unable to turn over in bed, and to sit up slowly in bed with assistance constituted a maximum effort. There was marked dyspnœa, disproportionately aggravated by talking and moving, and anorexia. A purpuric rash covered both legs and there was marked muscular fibrillation in the calves, thighs, and arms and to a lesser extent on the abdomen. The calves were tender. There was a mild conjunctivitis. The lower border of the liver was now palpable about two fingers' breadth below the costal margin. The blood pressure had dropped to 125/65. The neurological findings were unchanged with the exception of the ankle jerks which were no longer obtainable. At about the same time he started a moderate periodical pyrexia which proved to be due to an infection with *Brucella melitensis*. Hæmoglobin, 66 per cent. Urine normal. Fig. 2B showed significant changes

compared with the record taken in 1937 (Fig. 2A). There was sinus rhythm, rate 75. The initial ventricular deflections in the limb leads were considerably smaller and in lead III were directed upwards. The R–T intervals had become deformed and curved with their convexity directed upwards and in leads II and III and in the chest leads were depressed below the iso-electric line. T I had become flatter and in the remaining leads diphasic. Altogether the tracing exhibited features indicative of myocardial damage.

The patient was put on vitamin B1 injections, 10 mg. daily, also vitamin B1 by mouth, later supplemented by other vitamins (Medikap tablets 4 daily and Redoxon 50 mg. daily, the former being replaced later by Benerva compound tablets, 6 daily), iron (Fersolate, 6 tablets a day) and coramine (15–20 drops t.i.d.). He regained some strength very quickly, and when seen again after four days could easily turn over in bed, dyspnœa and appetite had considerably improved. The conjunctivitis



A B C

FIG. 2.--Case 2. (A) Aug. 17, 1937; (B) Feb. 7, 1942; (C) Feb. 22, 1942. Time markings: in (A) 1/25 sec. in (B) and (C) 1/25 and 1/5 sec.

had disappeared and the purpuric rash was fading. The muscular fibrillation, however, had increased in intensity and extent ; it improved only very slowly, disappearing after six months, and the Brucella infection took about eight months to clear up. The blood count improved steadily. The further convalescence was complicated by a thrombophlebitis in the right leg. The blood pressure remained low for a year, but reached 150/80 in April, 1943, and remained at that figure.

An electrocardiogram taken on the fourth day of vitamin treatment showed that the changes in the R–T portions described above had already become less marked, particularly in leads II and III; R I had increased and R III decreased in height; the rate had decreased to 70. After another 11 days of vitamin treatment Fig. 2C showed essentially the same features as the record taken in 1937 before the onset of vitamin deficiency (Fig. 2A), only that there was now a small upright T III; otherwise the signs of myocardial disease had disappeared although the *Brucella* infection was active throughout that period and on the evening before Fig. 2C was recorded the temperature had been 101·8. This observation illustrates that the electrocardiographic changes were specifically due to the vitamin deficiency. Accurate measurements of the duration of the electrical systole were not possible in this case.

Case 3. A man, aged 51. Admitted to Guy's Hospital on July 6, 1943, because of swelling of both legs and thighs, attacks of giddiness with collapse on several occasions and shortness of breath on exertion. The condition had started three months before admission and had gradually become worse. He had been out of regular work for ten years and had lived a precarious life as a tramp, having various occupations, some of which entailed much physical exertion, and he had long periods of malnutrition, usually living on tea, bread, butter, margarine, and jam, which he obtained at coffee stalls. He did not take any alcohol.

On examination he looked frail ; the skin had a slight yellowish tinge. The calves were very tender and there was œdema of both legs and thighs. The abdomen was distended and there was ascites; rales were heard over both bases. Hæmoglobin, 30 per cent; blood pressure, 140/65. The ankle jerks could not be obtained. There was achlorhydria. He was put on injections of vitamin B1, 5 mg. daily, ordinary diet and Blaud's pills and his condition improved rapidly. His urinary output was 35 oz. on the first day of vitamin treatment and during the following four days was 689 oz.

The tenderness over the calves and the dyspnœa improved in the course of a fortnight. After a week he developed diarrhœa which stopped when Blaud's pills were discontinued. From July 17, ascorbic acid (50 mg.) as well as vitamin A and D were added. On discharge on August 19 to a convalescent home he was free from symptoms.

Fig. 3A was taken on the fourth day of vitamin treatment and showed sinus rhythm, rate 87. The initial ventricular deflections in all standard leads were small, R I measuring 5 and R II 4 mm, and

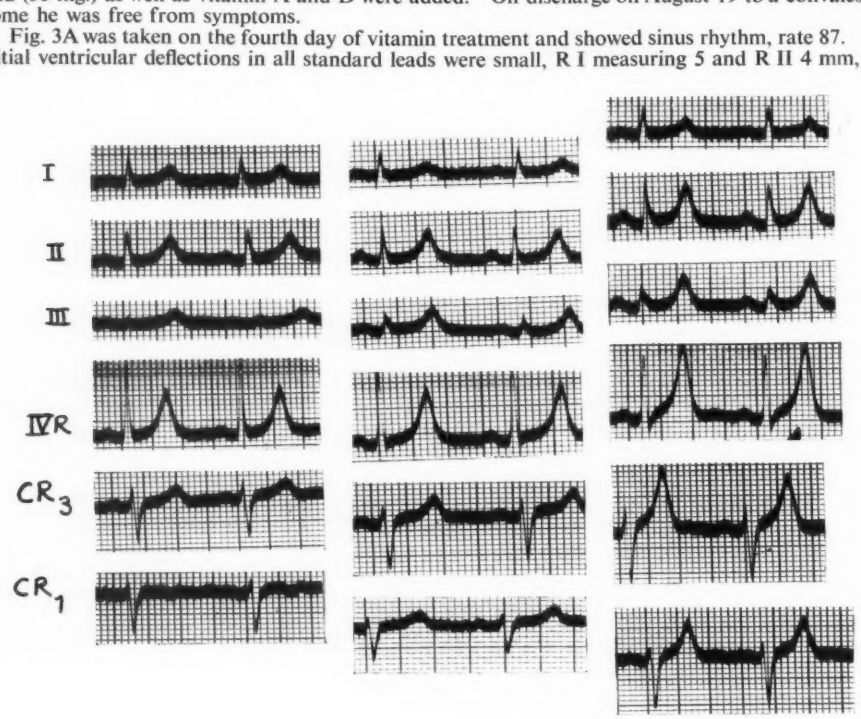


FIG. 3.—Case 3. (A) July 10, 1943; (B) July 13, 1943; (C) July 23, 1943. CR_1: right arm—right border of sternum at the insertion of the fourth rib. Time markings: 1/25 and 1/5 sec.

R III being almost invisible. In the right pectoral chest lead the T waves were inverted, otherwise the chest leads were normal. Fig. 3B, taken three days later, showed a rate of 77 and a marked increase in the height of R III and especially of T II and T III; in the right pectoral chest lead the T waves had become upright. Three days later these changes had become more marked, and a week after that there was another conspicuous increase in the height of the T waves in all the leads (except lead I) (Fig. 3C); in lead III and the apical chest lead the height of the T waves exceeded that of the R waves and in lead II they were equal in height. After another week the height of R III and of T II and T III and of the apical chest lead had decreased, and ten days later the record had remained unchanged, except that R III had become almost invisible and there was a small downward deflection instead, measuring less than 0·5 mm. The duration of the electrical systole was within normal limits throughout.

DISCUSSION

Each of the three cases showed some unusual features of general clinical or cardiological interest.

In Case 1 the outstanding symptoms were weakness, dyspnœa, a dry hacking brassy cough, and transient swellings of unusual distribution. Although a cough of this kind is known to occur in cases of vitamin B1 deficiency (Weiss and Wilkins, 1936, 1937) one does not usually associate it with this condition. Oedema of a similar distribution has been observed by Jones and Bramwell (1939), but is not usually of such transient character. In regard to the electrocardiogram, the T waves in leads I and the chest lead were unusually wide and at the same time flat and " dome-shaped " without a high take-off, the duration of the electrical

systole being markedly increased. A somewhat similar shape was found by Boyd Campbell and Allison (1940), and Weiss and Wilkins (1936, Fig. 3), but apparently is uncommon. The temporary inversion of the final deflections during the early stages of treatment with vitamin B1 has been reported by several authors (Boyd Campbell and Allison, 1940 ; Dustin Weyler, and Roberts, 1939; Weiss and Wilkins, 1936, 1937). Failure to recognize this as a temporary occurrence during vitamin treatment may result in a mistaken diagnosis of coronary disease, or even recent coronary occlusion. When subsequently the patient had a relapse and several clinical symptoms and signs of vitamin deficiency recurred the electrocardiogram remained normal. These observations are in keeping with the experimental findings of Weiss, Haynes, and Zoll (1938) that in rats fed on a vitamin B1 deficient diet temporary inversion of T occurred after the injection of vitamin B1 in some animals and that on repeated induction of vitamin B1 deficiency the cardiographic changes were not always identical. In dogs electrocardiographic changes were demonstrated by de Soldati (1940). Lengthening of the duration of the Q–T intervals in cases of vitamin B1 deficiency and a return to normal with adequate treatment was found by several authors (Dustin, Weyler, and Roberts, 1939; Goodhart and Joliffe, 1938; Weiss, 1940; Weiss and Wilkins, 1936, 1937; Dustin, Weyler, and Roberts, 1939), moreover, observed temporary increase at the beginning of treatment.

In Case 2 the onset of signs of vitamin B1 deficiency coincided with the onset of a *Brucella* infection. It is known that infections not infrequently precipitate the signs of beriberi which until then had remained latent (Aalsmeer and Wenckebach, 1929; Weiss, 1940). In the present case several factors known to precipitate the clinical manifestations of vitamin deficiency co-existed: a negligible intake of vitamin B1 due to gross dietary deficiency, and a high demand of this vitamin owing to the disproportionate amount of carbohydrate in the diet, the excessive consumption of alcohol, and the infection. Gross muscular fibrillation was a prominent sign and it is difficult to decide whether this was due to the vitamin deficiency, the *Brucella* infection, or the combination of the two. It disappeared after about six months of continual vitamin treatment, about two months before the last manifestation of the *Brucella* infection. Another conspicuous feature was marked dyspnœa at rest disproportionately aggravated by the slightest physical exertion. The circulatory factors responsible for this condition have been studied in detail by Hayasaki and Inawashiro (1928).

In Case 3 cardiac failure due to vitamin B1 deficiency occurred in a patient who did not take any alcohol, as a result of deficient diet only. Few such cases have been reported in this country (Konstam and Sinclair, 1940; Swan and Lewis, 1940; result of deficient absorption, Ungley, 1939). Physical exertion seems to have precipitated the onset; the importance of this factor is shown by the fact that cardiac failure is less likely to develop or is delayed in its onset in beriberi patients with paralysis (Keefer, 1930), and that severe polyneuritis is usually associated with only a mild degree of congestive circulatory failure (Weiss, 1940). Similar observations have also been made in experimental animals (Swank and Bessey, 1942; Swank, Porter, and Yeomans, 1941). The electrocardiographic findings in Case 3 resemble those of Katz (1941, Fig. 210), especially in respect of temporary gross increase in the height of the T waves in the chest lead.

It is noteworthy that in all three cases the chest leads showed changes, whereas in a series of six cases Dustin, Weyler, and Roberts (1939), found that the chest lead generally showed little disturbance. Changes in the chest leads seem to be more common in pellagra (Feil, 1936).

Summary

Three cases of circulatory disturbances due to vitamin B1 deficiency are described with special reference to some unusual clinical and electrocardiographic features. Two of the three patients took an excessive amount of alcohol, in the third case the condition was caused by deficient diet only. All responded to treatment with vitamin B1.

I wish to thank Dr. Geoffrey Marshall, under whose charge Case 3 was admitted to Guy's Hospital, for his permission to examine this patient and publish his notes.

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CARDIAC OUTPUT IN MAN BY A DIRECT FICK METHOD

Effects of Posture, Venous Pressure Change, Atropine, and Adrenaline

BY

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I. Effects of Posture and Venous Pressure Change

In the Fick method of estimating cardiac output (C.O.), where C.O. (litres/min.)=oxygen consumption (c.c./min.) divided by arterio-venous oxygen difference (c.c./litre), the measurement of the numerator can easily be made by spirometric methods. Hitherto the measurement of the arterio-venous oxygen difference in man by respiratory techniques has proved difficult and laborious, and it has not been possible to make frequent serial observations. The difficulties seem to be largely overcome by the method of cardiac catheterization first introduced by Forsmann (1929) and developed by Cournand and Ranges (1941). Over 394 catheterizations can now be recorded without any accidents (Forsmann (1), de Carvolho and Moniz (48), Ameuille *et al.* (60+), Cournand *et al.* (150) and the present authors (135)). The catheter has been left *in situ* as long as 24 hours (Cournand *et al.*), but the present authors have limited the period to one hour in normal subjects. Clotting does not occur on the unwettable surface of the catheter, and a slow drip of 3·8 per cent sodium citrate through the catheter prevents any thrombus formation round the hole at the tip.

Method

The observations were made on normal male volunteers about two hours after the midday meal. The subjects were supine, except where otherwise stated. A No. 12 radio-opaque ureteric catheter was introduced through a wide bore needle into the medial antecubital vein of the left arm. The introduction was painless. Usually the catheter passed smoothly into the right auricle where its position was verified by X-ray. In about one subject in seven an obstruction was encountered at the root of the neck, but gentle manipulation may allow passing the catheter to the desired position. Occasionally the catheter took an acute turn up into the left internal jugular vein. The catheter was attached to a citrate manometer which recorded changes in pressure in the right auricle and served to keep the catheter clear of blood; 15 c.c. samples of right auricular blood were withdrawn under oil for estimation of oxygen unsaturation. No accidents or complications have followed this procedure except sometimes an inch or so of thrombosis near the point of insertion in the arm vein.

Oxygen unsaturation of right auricular blood was estimated in a Haldane blood gas apparatus modified to take 6 c.c. samples. The oxygen capacity was estimated by hæmoglobinometry. When the lungs were normal a value of 95 per cent saturation was assumed for arterial blood and the arterio-venous oxygen difference calculated from this assumption. The estimation of oxygen unsaturation was made at room temperature, at which the oxygen consumption was also measured by a Benedict spirometer. This simplifies the calculation considerably. The arterio-venous oxygen differences quoted below are uncorrected for N.T.P.

In the recumbent position the mean right auricular pressure (R.A.P.) is recorded with the posterior surface of the thorax equal to zero level. The pressure averages approximately 14 cm. anterior to this point (Richards *et al.* 1942).

Results

Normal values.—As will be demonstrated in the second section, heart rate influences resting output, and for this reason we tabulate as " normal " values in which the pulse rate was under 80 per minute. Numbers are as yet too few to establish a statistical mean and range, and data may conveniently be grouped as follows:—

TABLE I

Arterio-venous oxygen difference (c.c./litre)	Number
30–40	3
40–50	10
50–60	4

Cournand *et al.* (1943) give a mean figure of 45 c.c./litre for the arterio-venous oxygen difference. Baumann (1930) by heart puncture got an average figure of 51·5 c.c./litre.

Posture. In 17 subjects the cardiac output was estimated in the erect and supine positions. Samples were taken while subjects were standing quietly immediately after X-ray screening. The actual oxygen consumption in this position was not measured, but previous data (McMichael, 1937; Grollman, 1932; Nylin, 1934) indicate the average value to be 14 per cent over the recumbent oxygen consumption rate. Results are shown in Table II. It is seen that cardiac output increases by an average of 33 per cent on lying down. This agrees with the bulk of previous work (see Hellebrandt and Franseen (1943) for references) and refutes the recent suggestion of Starr and Rawson (1941), based on the ballisto-cardiograph, that there is no change.

TABLE II

Postural Changes in Arterio-Venous O_2 Difference

(14 subjects)

Arterio-venous O_2 difference (c.c./litre)	Recumbent	45 30 34 42 52 42 36 30 42 46 41 44 34 40. Average: 40
	Standing	60 66 53 70 65 49 62 43 75 57 61 72 53 65 Average: 61
	Average O_2 consumption c.c./min.	Recumbent: 240. Standing: 274
	Cardiac output/min.	Recumbent: 6 litres. Standing: 4·5 litres

Change in right auricular pressure. The venous pressure can be conveniently raised by intravenous infusions of saline (Sharpey-Schafer and Wallace, 1942) and lowered by venesection (Wallace and Sharpey-Schafer, 1941) or by cuffs on the thighs at diastolic blood pressure. Sample data from observations of these types are shown in Fig. 1, 2, and 3, and

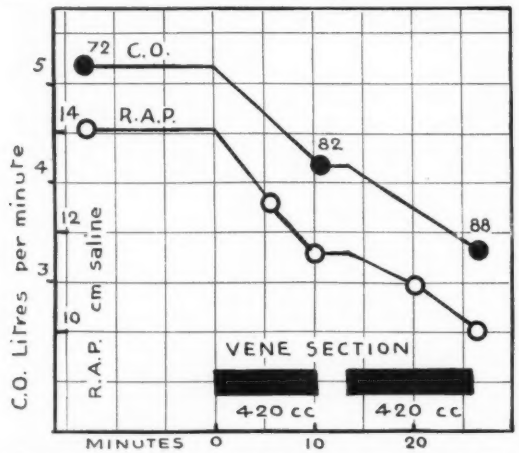

Fig. 1.—Effect of venesection on cardiac output and right auricular pressure. In Fig. 1, 2, and 3 figures beside cardiac output determinations indicate heart rate. Right auricular pressure (R.A.P.) and cardiac output (C.O.) fall in parallel.

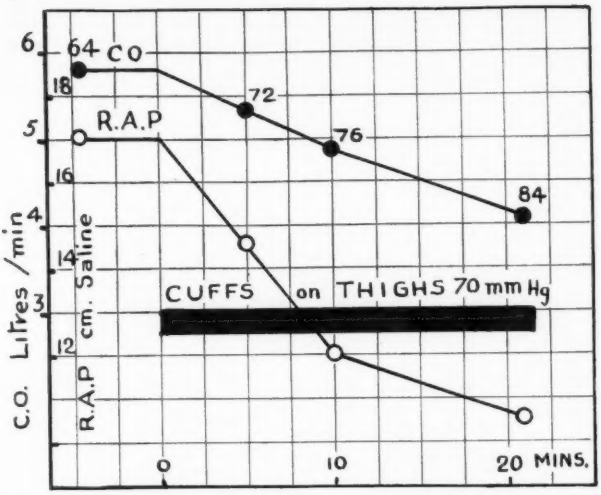

FIG. 2.—Effect of tourniquets on both legs at 70 mm. Hg. Blood is trapped in the leg veins, right auricular pressure (R.A.P.) and cardiac output (C.O.) falling together.

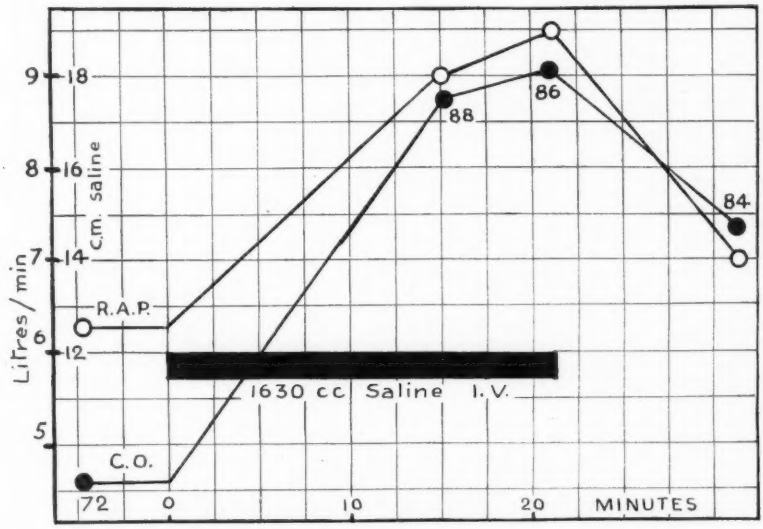

FIG. 3.—Effect of raising right auricular pressure (R.A.P.) by saline infusion. During infusion the cardiac output (C.O.) rises. On stopping the infusion saline is lost from the circulation and right auricular pressure and cardiac output fall together.

the collected data from all observations are shown in Fig. 4. As expected from Starling's law of the heart, a reduction in right auricular pressure leads to a fall in cardiac output, while a rise is accompanied by an increase.

DISCUSSION

Taking all our available data into account, the average normal resting cardiac output in the recumbent position is (240/45) 5·3 litres a minute, while in the standing position it is 25 per cent less, i.e. 4 litres. These are higher than figures previously obtained by the

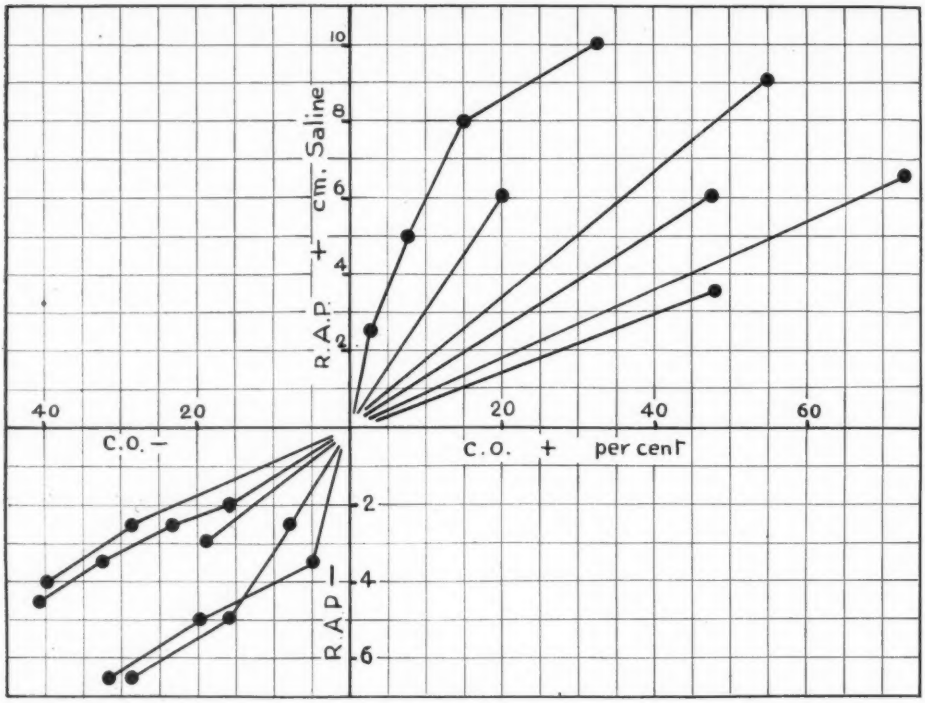

FIG. 4.—Collected data in 11 subjects showing increasing cardiac output (C.O.) with intravenous infusion and decrease with venesection or cuffs on legs.

acetylene technique, which gave an average cardiac output in the recumbent position of 4 litres a minute (McMichael, 1937): it is of interest, however, that two techniques then used gave an average increase in cardiac output of 32 per cent and 38 per cent in recumbency, which compares well with 33 per cent by the new method. Relative changes seem to have been fairly accurately reflected, but the absolute values were subject to a systematic error.

The assumption of 95 per cent arterial oxygen saturation in these observations may be criticized. Our aim has been to simplify the technique as much as possible for application to clinical problems, and *repeated* arterial punctures do not seem to be justified. For following *changes* in any individual under test the assumption can lead to little significant error. A range of 93–97 per cent oxygen saturation of arterial blood would give a standard error of 2 c.c. per litre in the arterio-venous oxygen differences.

II. Effects of Atropine, Adrenaline, and Heart Rate

The methods and conditions of study were the same as in the first part.

Atropine. Observations were made in 10 subjects. Two main effects were found. Raising the heart rate increased cardiac output in all subjects except two, and there was a fall in right auricular pressure (R.A.P.) in all (Fig. 5). Atropine was given intravenously in doses of 1 mg. and the usual sequence of events was as follows: within 30 seconds the heart rate was increasing, reaching its maximum rate in about 1–2 minutes; at this point the cardiac output was considerably increased; the R.A.P. fall was slower in appearing and only attained a steady level after a few minutes. Fig. 6 shows that this fall in right auricular pressure may be accompanied by a decrease in cardiac output from the high level attained

earlier by atropine. In two out of ten observations no rise in cardiac output was observed at the time of sampling. It would appear that a large fall in R.A.P. was sufficient to prevent

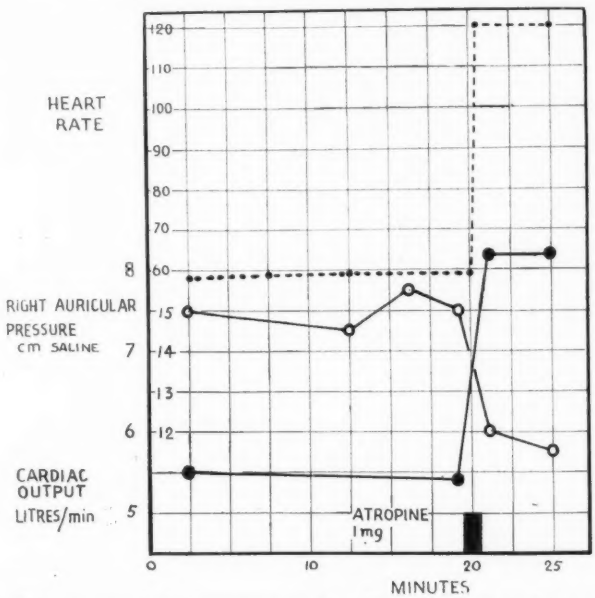

FIG. 5.—Usual immediate response to intravenous atropine. Heart rate and cardiac output increase, right auricular pressure falls.

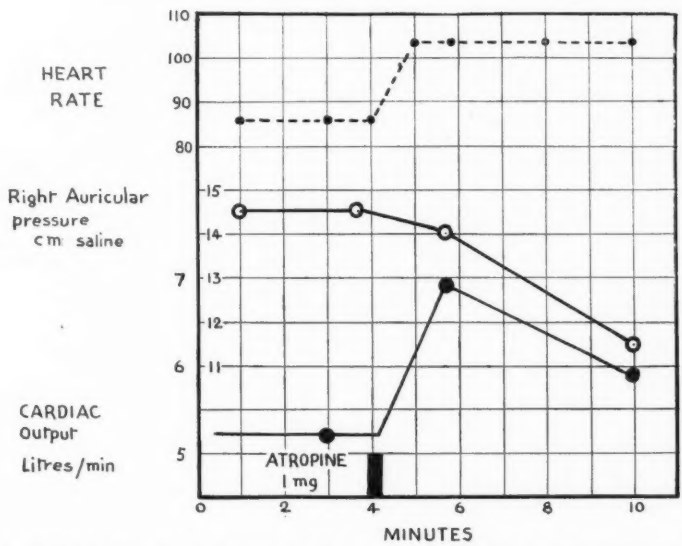

FIG. 6.—Showing initial increase in cardiac output after atropine followed by a fall as right auricular pressure decreases.

the usual rise of cardiac with atropine acceleration (Fig. 7). These results indicate that the effects of acceleration of the heart rate increasing cardiac output may be modified by venous pressure changes.

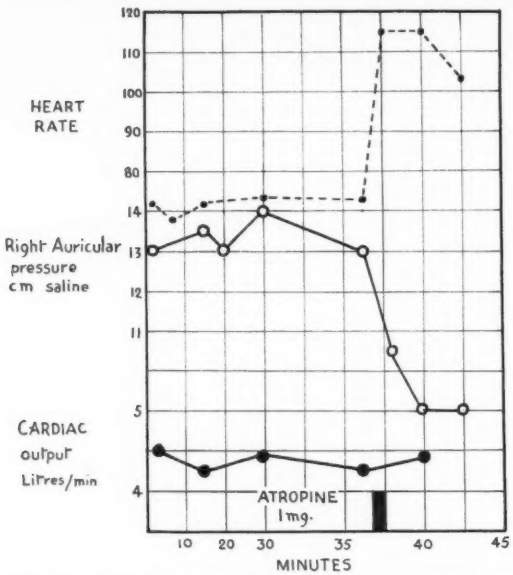

FIG. 7.—Showing no increase in cardiac output after atropine with considerable fall in right auricular pressure.

Adrenaline. We studied the effects of doses that, infused intravenously, did not raise the blood pressure or increase the heart rate. Such doses were under 10μg. a minute, but the suitable dose for each individual may have to be found by trial. Dilatation of muscle vessels is produced by adrenaline administered in this dosage, and in some experiments this

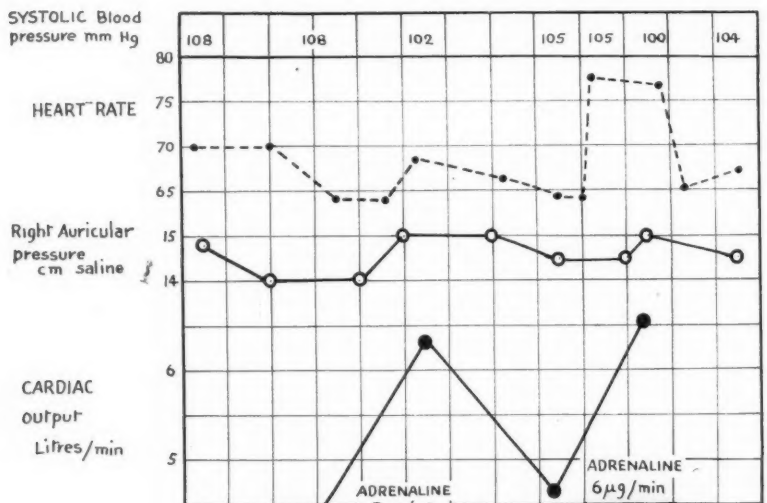

FIG. 8.—Effect of adrenaline infusion at 3μg. a minute. Cardiac output increases without change in heart rate or right auricular pressure or rise in blood pressure. When the dose of adrenaline was doubled, the heart rate increased.

effect was demonstrated by Professor H. Barcroft and Dr. O. G. Edholm, who simultaneously measured forearm flow with a Lewis-Grant plethysmograph. In all of 5 subjects adrenaline increased cardiac output, and a typical observation is shown in Fig. 8. On stopping the infusion, cardiac output returned rapidly to the resting level. Slight pallor of the face was observed during infusion, and some subjects became conscious of the beating of their hearts. Conspicuous flushing of the face appeared when the infusion was stopped. The results show that adrenaline can increase cardiac output without a change in venous pressure or heart rate.

Heart rate. The total data on cardiac output determinations in normal subjects are shown plotted against heart rate in Fig. 9. The majority lie between 4 and 6 litres a minute, while

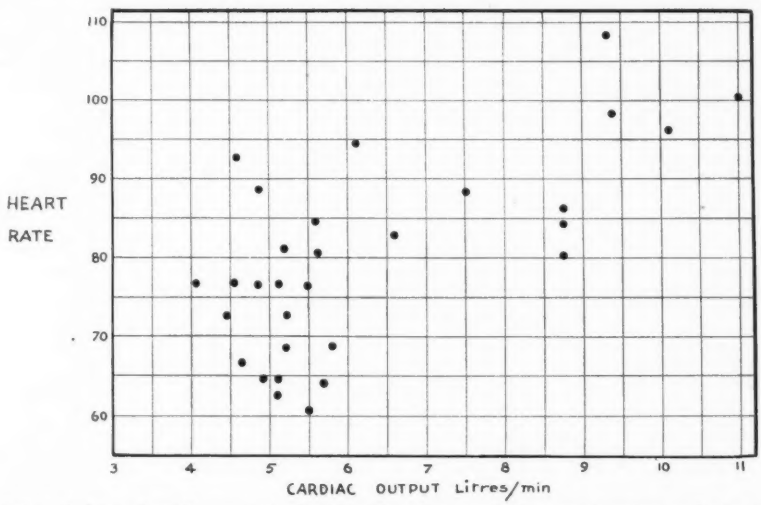

FIG. 9.—Collected data of cardiac output plotted against heart rate in normal resting males in the supine posture. The few with higher outputs show faster heart rates.

a few have higher outputs up to 10 or 11 litres a minute. It will be seen that the latter group tends to have faster heart rates, and this may be one factor in causing increased output. Other possible factors such as secretion of adrenaline or slightly increased venous pressure could not be compared from subject to subject. All those with increased output were in the younger age groups (under 40), when the circulation might be expected to be more labile.

DISCUSSION

There is a mass of physiological evidence that right auricular pressure, determining tension and length of myocardial fibres, is the major factor altering the output of the heart provided the rate remains constant. The first part of this work shows such effects in man, although rate and other factors for obvious reasons could not be controlled.

Wiggers (1938) indicates that within the usual physiological range increased rate leads to increased minute output so long as the venous pressure is kept constant. We have as yet no explanation to offer for the fall in right auricular pressure observed so often after atropine. Its late onset indicates that it may be a physiological adjustment secondary to the initial increase in output.

Independently of rate and right auricular pressure, the adrenaline effects indicate yet another mechanism controlling cardiac output. Adrenalin produces increased systolic ejection at the same mean filling pressure in the right auricle. This is in accordance with the observation of Wiggers (1927) that adrenaline causes a stronger and more rapid ventricular contraction and also a more complete relaxation in diastole.

Summary

Serial estimations of cardiac output and right auricular pressure can be made by means of a ureteric catheter passed along the veins into the right auricle.

Normal resting values for arterio-venous oxygen differences were rather lower than those obtained previously by the acetylene method.

Cardiac output in the supine posture showed a 33 per cent increase over that in the erect.

A fall in right auricular pressure reduced, and a rise in right auricular pressure increased, the cardiac output.

Acceleration of the heart with atropine usually increased cardiac output and caused a fall in right auricular pressure. Occasionally the fall in right auricular pressure may operate against an increase in cardiac output.

Intravenous adrenaline increased cardiac output in doses that did not accelerate the heart or raise the blood pressure.

Normal subjects with high resting outputs had faster heart rates than the others.

We wish to thank the volunteers from the Friends Ambulance Unit. The Medical Research Council defrayed our expenses.

We are indebted to the staff of the Radiological Department and to Mr. A. H. Latham for their technical aid.

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THE HEART IN MYOTONIA ATROPHICA

BY

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Myotonia atrophica is a familial complaint appearing in young adult life. Atrophy of muscles is conjoined with increased tone. Early baldness, with wasting of the temporal, facial, and sterno-mastoid muscles when the disease is fully developed, give to the patient a characteristic appearance (Fig. 1). Atrophy also takes place in the girdle and limb muscles.

FIG. 1.—Two patients (Cases 7 and 13) showing characteristic features of myotonia atrophica.

Increased tone is illustrated by the delayed relaxation of the hand-grip, by dimpling of the tongue when struck by a spatula or by a patella hammer against the lower teeth, and by the adduction jerk of the thumb when the thenar eminence is struck. Cataract (seen only by the slit-lamp during the early years of the disease) and atrophy of the testes with impotence are other characteristic findings. The condition is not uncommon, but because such obvious changes are absent during the early stages of the illness, it may go unrecognized for many years. The medical history of patients in whom I examined the heart convinced me of the need to implement the myopathic signs with others that might lead to an earlier diagnosis and spare the patients the unfair judgment passed on them by employers and doctors alike in regarding them often as nervous subjects or even malingerers. I found that signs discovered during the examination of the cardiovascular system contribute to the surer and earlier diagnosis of myotonia atrophica.

In the English literature dealing with myotonia there is little reference to its effects on the heart. Adie and Greenfield (1923) described 20 cases and mentioned that in one examined at necropsy the heart was healthy and in another the electrocardiogram was normal ; this led them to say that the observation of the heart being affected in myotonia lacked confirmation. It was Maas and Zondek (1920) who first wrote about involvement of the heart,

reporting cardiac enlargement in one case which also showed sinus bradycardia and a prolonged P–R interval, and similar changes in the cardiogram of two other patients. In seven patients examined by Guillain and Rouquès (1932) the P–R period was slightly prolonged in two only. Sinus bradycardia was the only change noticed by Havier and Decourt (1933) in one case, but in another reported by Mondon and Pasquet (1939) the P–R interval was long and the T wave was inverted in lead I. Two out of three young patients with myotonia described by Carrillo (1941) had abnormal cardiograms, showing low voltage of the P wave, long P–R interval, wide and notched QRS complex, and left axis deviation. Segura and Lanari (1941), on the other hand, described eleven patients with different forms of myotonia in whom clinical, cardiographic, and radiological examination had shown no abnormality of the heart, while microscopy in one instance demonstrated a healthy myocardium.

In order to test these different opinions on the state of the heart in myotonia atrophica, thirteen cases were collected for special examination. Ten were males and three females. Their ages varied from 23 to 45 and the average age was 35 years. Each had been diagnosed by a neurologist as a typical case of myotonia atrophica.

Cardiac symptoms. The most prominent symptoms were always those identified with the myopathy. Two patients (Cases 12 and 13), in whom the heart was enlarged, complained of breathlessness but neither showed signs of heart failure. Two attacks of unconsciousness in one patient (Case 12) had the features of Stokes-Adams attacks although they were not directly observed. None complained of heart pain.

The pulse. In only two cases was the pulse slow and in one of these the sinus bradycardia alternated with heart block. The force of the pulse was often noticeably small and this change was so common (8 out of 13) as to suggest that it is a characteristic sign in myotonia atrophica.

The blood pressure. The blood pressure was not raised in any of the 13 cases. It was highest (160/70) in Case 13 during periods of 2 : 1 heart block. In five it was low and in three of these the systolic pressure was 95 or under (see Table I). In one case administration of desoxycorticosterone acetate raised the blood pressure and this effect is shown in Fig. 2. It is not maintained that this is a specific effect in myotonia atrophica and there was no change

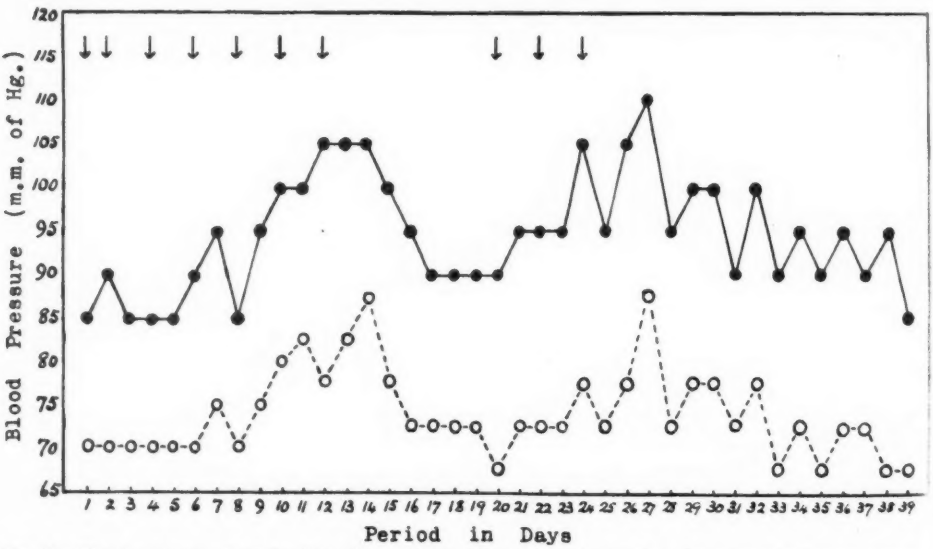

FIG. 2.—Blood pressure chart in Case 12 to show effect of treatment by, desoxycorticosterone acetate (D.O.C.A.). Continuous line represents systolic and discontinuous line diastolic pressure. Arrows indicate intramuscular injection of 10 mg. of D.O.C.A.

TABLE I

CARDIOVASCULAR CHANGES IN 13 CASES OF MYOTONIA ATROPHICA

Case No.	Age	Pulse		Blood Pressure	First Heart Sound	Voltage of P Wave	Electrocardiographic changes			Size of heart at cardioscopy
		Rate	Character				P–R interval (sec.)	Notching of QRS	Other changes	
1	23	70	Normal	120/85	Normal	Low	0·20	Absent	Deep Q in III.	Normal
2	29	90	Small	120/95	Splitting	Normal	0·20	,,	— — —	Appears small
3	31	70	Normal	115/80	Distant	Low	0·20	Present	Left axis deviation	Normal
4	31	100	Small	125/100	Splitting	Normal	0·21	,,	Variation in electrical potential	,,
5	45	70	,,	135/85	,,	Low	0·21	,,	Left axis deviation. Variation in electrical potential	,,
6	36	85	Normal	140/85	Normal	,,	0·21	,,	T flat in I. S deep in I and II	,,
7	42	85	Small	90/80	Splitting	Normal	0·22	,,	T low in I. Left axis deviation. Variation in electrical potential	Appears small
8	31	75	,,	110/85	Normal	,,	0·22	,,	— — —	,, ,,
9	31	82	,,	95/80	Splitting	,,	0·24	,,	Left axis deviation	,, ,,
10	32	85	,,	120/75	,,	Low	0·25	,,	,, ,,	Slight enlargement
11	41	50	Normal	125/95	Distant	,,	0·26	Absent	,, ,,	,, ,,
12	41	72	Small	85/75	4th heart sound	,,	0·30	Present	Atypical bundle branch block	Moderate ,, enlargement.
13	44	37 to 48	Normal	160/70	Systolic murmur	,,	0·31 or 2 : 1 block	,,	Left axis deviation Deep Q and S in I	,, ,,

in the myopathic signs although the patient felt much better during the time the blood pressure was raised by the adrenal therapy.

The first heart sound. Impurity of the first heart sound was a common finding and the sound was normal in three cases only. The association of splitting of the sound with a prolonged P–R interval in the cardiogram is shown in Table I. Once a prolonged P–R period gave rise to a triple rhythm from the addition of the fourth heart sound.

Cardiographic changes. A lengthened P–R period was the commonest change in the electrocardiogram. In none of the thirteen cases was the period less than 0·20 sec.; it was 0·24 or greater in five and in two patients it measured 0·30 and 0·31 respectively. In the last case, 2 : 1 heart block was more often present than sinus rhythm (Fig. 3 and 4). In two,

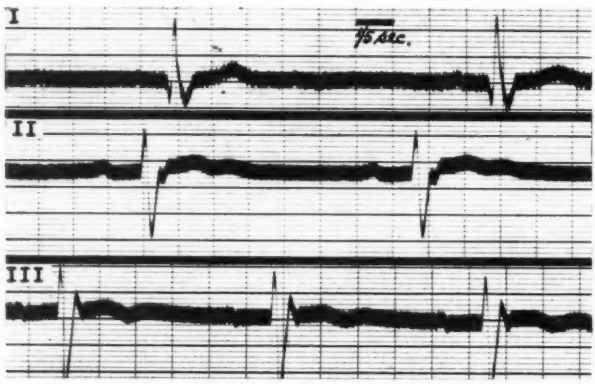

FIG. 3.—Cardiogram in Case 13 during phase of sinus bradycardia. Prolonged P–R period. Small P waves. Slurring of QRS complexes.

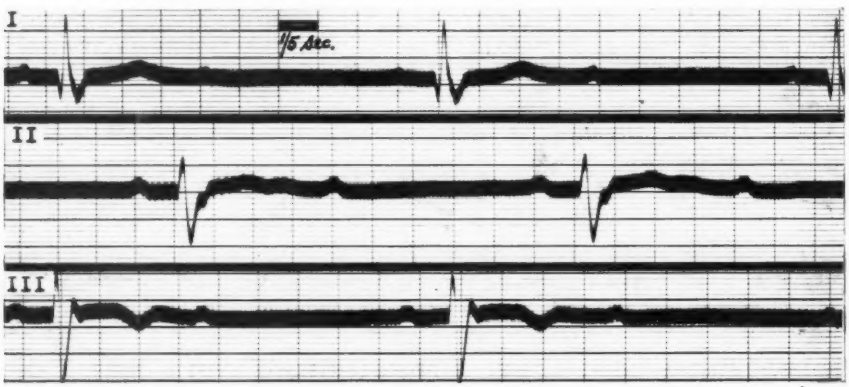

FIG. 4.—Cardiogram in Case 13 during phase of 2 : 1 heart block.

injection of atropine and tachycardia induced by glyceryl trinitrate did not affect the length of the period. Notching of the QRS complex was another common cardiographic abnormality and it was present in nine patients. The Q–S interval, however, was only once greater than 0·10 sec. when it was 0·15 (Fig. 5), giving to the tracing the appearance of left bundle branch block, but unlike such a curve, the T wave was upright in leads I and CR_7. A low voltage of the P wave was the third characteristic change in the electrocardiogram of myotonia atrophica (Fig. 5 and 6); it was present in eight. In the remaining five, the P in lead I was invariably low, but as it was normal in one of the other leads it has not been counted as an

abnormal change. Thus, a well-formed P wave in lead I is an unlikely finding in the cardiogram of a patient with myotonia atrophica. Left axis deviation (Fig. 6) was another common finding (7 out of 13). This was found in the absence of hypertension; it was present when

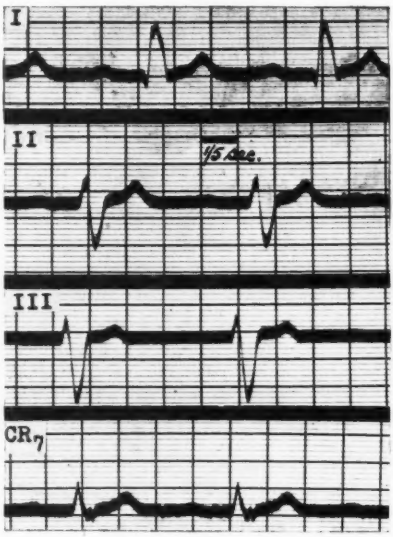

FIG. 5.—Cardiogram in Case 12. Unlike left bundle branch block, T is upright in leads I and CR_7. Prolonged P–R period. Small P waves.

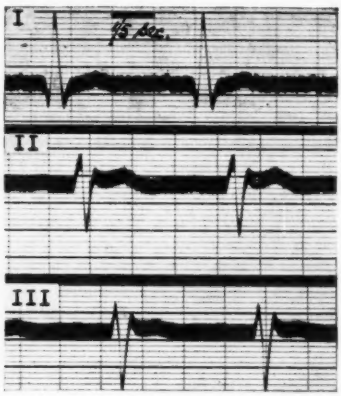

FIG. 6.—Cardiogram in Case 10 showing left axis deviation. Prolonged P–R period. Small P waves.

the blood pressure was low, although it was a feature in three of the four patients in whom the heart was found enlarged at cardioscopy. In two there was no enlargement and the heart appeared to be small in two other cases. Three patients showed a varying electrical potential of the QRS complexes (Fig. 7). It is not suggested that this is a change common to

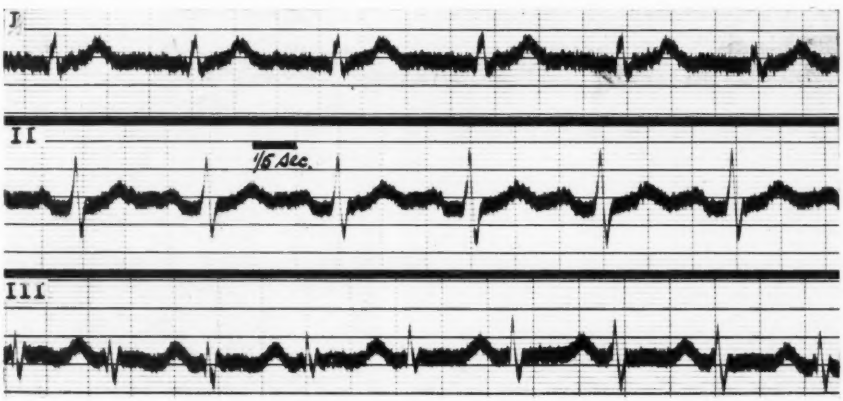

FIG. 7.—Cardiogram in Case 4 showing prolonged P–R period, slurring, and varying electrical potential of QRS complexes.

myotonia for it is not infrequently seen in tracings from healthy subjects, although the incidence of this sign in this series (3 in 13) is somewhat high. Changes in the Q, S, and T waves were inconstant and they have been listed in Table I.

Neither characteristic lens opacity (present in seven), family history of the complaint (common to eight cases), age of the patient, duration of symptoms (over five years in five),

FIG. 8.—Teleradiogram in Case 8. Heart shadow is small in relation to size of chest.

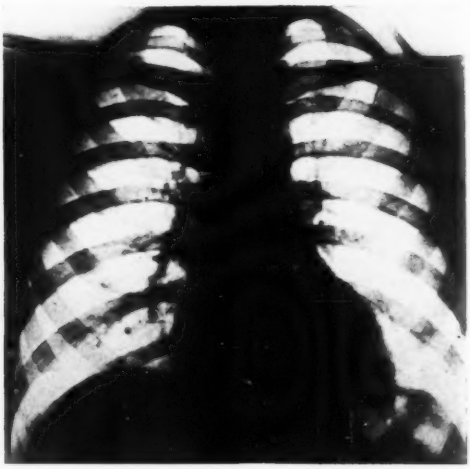

FIG. 9.—Teleradiogram in Case 11 showing slight cardiac enlargement.

nor the severity of the myopathic symptoms, appeared to determine the presence of such cardiographic irregularities.

Size of the heart. No obvious cardiac enlargement could be made out in any of the cases on clinical examination, although the apex beat was a little displaced outwards in two. The actual size of the heart, therefore, was estimated at cardioscopy. In five patients it was judged to be normal, and in four, smaller than was expected when age and stature received

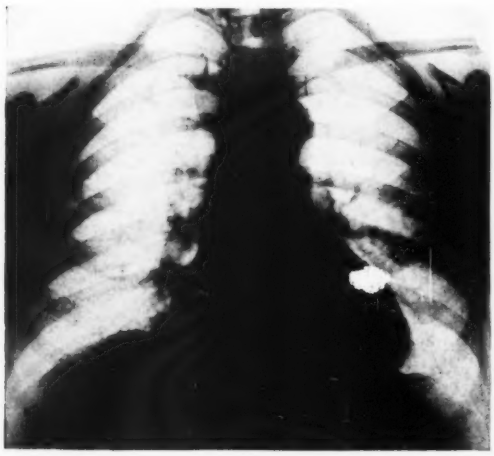

FIG. 10.—Teleradiogram in Case 12 showing moderate cardiac enlargement.

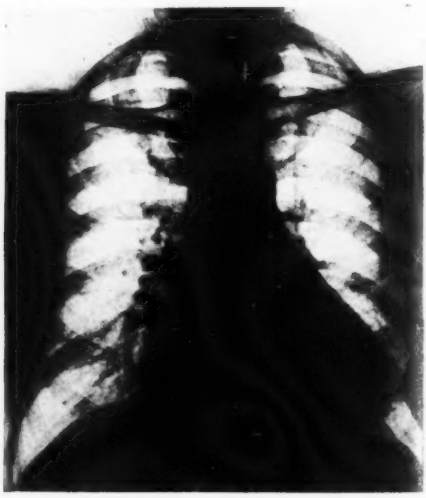

FIG. 11.—Teleradiogram in Case 13 showing moderate cardiac enlargement.

due attention (Fig. 8). In the remaining four the heart was enlarged, slight in two (Fig. 9) and moderate in two (Fig. 10 and 11). The presence of cardiac enlargement was closely

related to, if not dependent on, the length of the P–R period. Thus, when the P–R was 0·24 sec. or less, the heart was not enlarged; in the two cases showing slight enlargement the P–R interval was 0·25 and 0·26, and 0·30 and 0·31 sec. in two others in whom the heart was moderately enlarged. These last two complained of breathlessness on exertion, but there was no evidence of heart failure in either.

Summary and Conclusions

Examination of the heart in 13 cases of myotonia atrophica has shown that the presence of cardiovascular signs may help in the earlier diagnosis of the condition.

The pulse is often small and occasionally infrequent. The blood pressure is sometimes very low. The first heart sound in the mitral area commonly shows splitting, and sometimes triple rhythm may appear from addition of the fourth heart sound, this depending on the degree of elongation of the P–R period.

The changes that commonly characterize the electrocardiogram include elongation of the P–R period, low voltage of the P wave, slurring of the QRS complex, and left axis deviation.

The size of the heart varies so that it may be normal or may appear small, but in the presence of considerable lengthening of the P–R period, moderate enlargement takes place.

I wish to thank Dr. John Parkinson, Physician to the Cardiac Department, for his helpful criticism of this paper, and also several colleagues who kindly referred to me cases for this investigation.

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SYNCHRONOUS HEART SOUND RECORDING BY APPLICATION OF A SECOND CHANNEL TO THE COSSOR-ROBERTSON CARDIOGRAPH

BY

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By using a microphone to provide the input, the standard Cossor-Robertson cardiograph can be used to record heart sounds instead of the electrocardiogram, but such a record is of little value unless it is recorded synchronously with an electrocardiogram. For this purpose two separate recording channels are necessary. The double-beam cathode ray tube with two amplifying channels has been developed by Donovan (1943). With the addition of stationary spots and a moving-film camera to avoid loss of focus and definition due to curvature of the tube face, this is the method of choice. The possibility of replacing the standard single-beam tube of the Cossor-Robertson cardiograph with a double-beam tube was therefore investigated, but unfortunately it was found that the necessary alterations involved almost complete rebuilding of the instrument.

It is possible, however, to record simultaneously two different wave forms with a single-beam tube by using two valve amplifiers and an automatic switch which connects their outputs alternately to the single deflecting plate of the tube. The effect which this gives is illustrated in Fig. 1. If the switching rate is sufficiently high the gaps in the traces become small com-

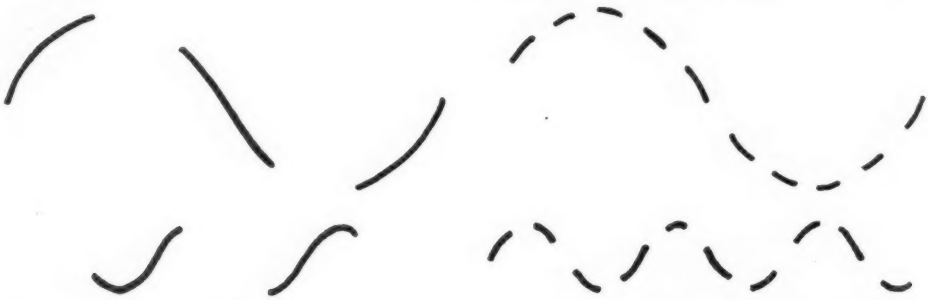

FIG. 1.—*Action of Switch.* (A) slow, and (B) more rapid switching rate. As the switching rate is increased the wave form becomes more accurately outlined.

pared with the spot size and each trace appears to be continuous. The passage of the spot from one trace to the other is so rapid that it is not visible. Such switching may be carried out either mechanically or by a thermionic valve device—the electronic switch. Mechanical methods cannot easily provide a switching rate that is sufficiently rapid to record the frequencies of heart sounds and murmurs, but a very efficient type of electronic switch was designed by Clothier (1939). The Clothier circuit is capable of switching between the two

recording channels 2500 times a second, and this very rapid switching rate can be used because the cathode-ray tube provides a recorder free from inertia and with an instantaneous response. The highest frequency that can be adequately recorded depends upon the switching rate (Fig. 1) ; with a rate of 2500 a second it is possible to record satisfactorily the wave form of frequencies up to 200 cycles a second, which is more than adequate for electrocardiography and quite sufficient for cardiophonography. Much higher frequencies can, of course, be recorded, but their wave form will not be completely outlined. With reasonable precautions in design there is no coupling between the two recording channels, so that a potential fed into one amplifier has no influence upon the other trace (Fig. 3).

The Clothier switch can be applied to the Cossor-Robertson cardiograph by connecting the output of its amplifier and the output of an external heart sound amplifier to the switch input. The switch output is connected to the cathode-ray tube. The entire recording system of the cardiograph is used without modification.

Modification of the Cossor-Robertson Cardiograph Recorder Unit

The required alteration is simple, and Messrs. Cossor kindly undertook to carry it out to meet our requirements. It is only necessary to divide the lead from the cardiograph amplifier to the cathode-ray tube, and to bring both ends to terminals on the case ; it is then possible to connect the output of the cardiograph amplifier to the Clothier switch by one terminal (A2),

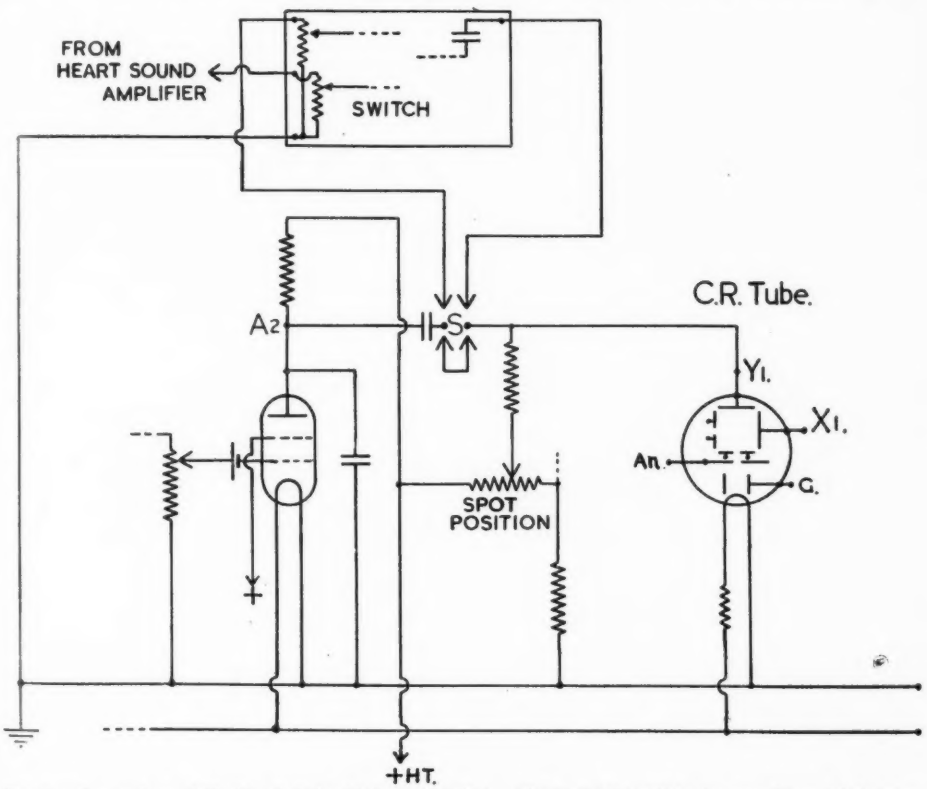

FIG. 2.—*Connections of Clothier Switch with Recording Unit.* The lead A2 to Y1 in the recorder unit is broken and the two ends brought to the central terminals of a double-pole double-throw switch (S). The switch then permits them to be connected together, restoring the circuit to its original form, or allows Y1 to be connected to the switch output, and A2 to one switch input, as used in the double-channel recorder.

and the switch output can be taken to the cathode-ray tube by the other terminal (Y1). These terminals were fixed on the back of the recorder unit. When Y1 and A2 are connected together the instrument is restored to its original condition and can be used in the ordinary way as a portable cardiograph. It is convenient to incorporate a double-throw double-pole switch so that a single movement converts the simple cardiograph to the double-channel recorder. The connections are shown in Fig. 2. One point of importance must be noted. The introduction of an extra valve in the amplifying system produces a phase shift of 180 degrees in all the potentials amplified. Thus if the deflections of the electrocardiogram are to appear in the same sense as that in which they are normally recorded the patient leads must be reversed.

The Clothier Electronic Switch

It is unnecessary to describe this here for full details have been published by Clothier (1939) and its application to medical purposes has been described elsewhere by one of us (Dawson, 1941).

The Heart Sound Amplifier

A simple resistance-capacity coupled amplifier is suitable, provided it has a frequency response up to 1000 cycles a second, and a gain of 50,000 to 100,000 times. To eliminate slow vibrations, such as movements of the chest and the cardiac impulse, low-frequency filtering is necessary, and this can be introduced by using interstage coupling of suitable value. The degree of attenuation of the lower frequencies depends on the product of the sizes of the grid condenser and the grid leak and, when the values are taken in microfarads and megohms, the product is the time-constant of the coupling. An overall time-constant for the amplifier of 0·1 sec. will attenuate a sine wave of 10 cycles a second by less than 5 per cent. This is the best response likely to be needed in cardiophonography, and increased low-frequency attenuation can be obtained, if required, by switching in grid condensers of smaller values in a single interstage coupling.

When a crystal microphone is used a very simple and satisfactory method of filtering is possible. The impedance of such a microphone is almost purely capacitative and, if the resistance of the load into which the microphone works is reduced, selective attenuation of the low frequencies occurs. The parallel connection of a variable resistance of 1 or 2 megohms allows continuous variation of low-frequency response. The inaudible low components of the heart sounds and of chest pulsations can then be reduced to any desired size.

The connections between recorder unit, Clothier switch, and heart sound amplifier are illustrated in Fig. 2.

Arrangement of the Traces

In order to keep the Cossor-Robertson cardiograph as compact as possible the back of the fluorescent screen is photographed through the side wall of the cathode-ray tube. Light from an image on the upper part of the screen passes very obliquely through the side wall of the tube and this leads to slight blurring of the photographic record owing to the formation of a double image. This is an intrinsic disadvantage of side-tube photography, and can only be overcome by direct photography of the front of the screen. In designing a portable cardiograph the slight blurring of the record when using side-tube photography has been justly regarded as of much less importance than the great increase in bulk which is inevitable when the front of the screen is photographed, and in practice the blurring is largely overcome by using only the lower two-thirds of the screen. In heart sound recording, however, a greater degree of sharpness is advisable and this can be obtained by using only the lower third of the screen from which light passes much less obliquely to the camera. The electrocardio-

gram was, therefore, arranged to occupy the middle third of the screen and the cardiophonogram was placed on the lower third. With side-tube photography it is never possible to obtain records comparable in clarity with those obtained by direct photography of the front of the screen, but it will be seen that this method gives images which are sufficiently clear for most purposes.

The separation of the two traces is controlled by the difference in grid bias of the two switching valves. The two traces tend to set themselves equidistant from a line, the position of which is controlled by the spot position control of the recorder unit. They can thus be moved down to the appropriate position without affecting their separation.

Records

Examples of the records obtained are illustrated in Fig. 3. The input was from a crystal microphone similar to the Cossor cardiophone but with a larger diaphragm opening, which we prefer. It will be noticed that the more rapid deflections of the heart sound records are

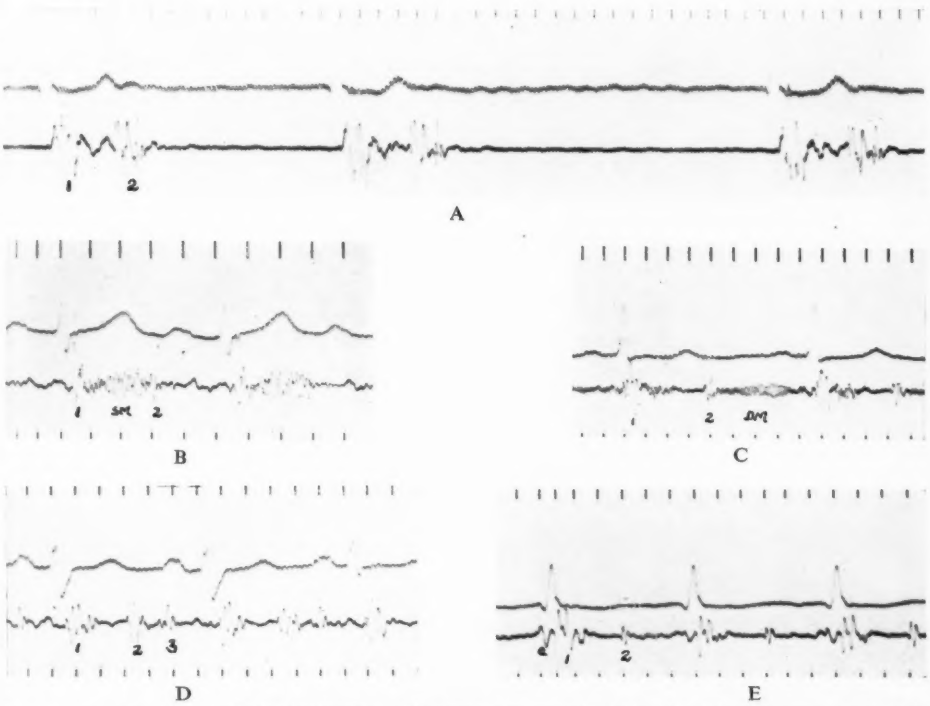

FIG. 3.—*Records*. (A) Auricular fibrillation. (B) Systolic murmur (S. M.). (C) Diastolic murmur (D. M.). (D) Triple rhythm due to audible third heart sound. (E) Abnormal first heart sound with auricular component (*a*) which precedes the peak of R. (Time marker : 1/10th sec.).

discontinuous. This is due to the flick of the spot from the cardiophonogram to the electrocardiogram. It will be clear from Fig. 1 that exact vertical alignment (i.e. synchrony) of the traces is automatic and accurate provided that the axis of the tube is set so that the displacement of the spot is truly vertical. It is normally set accurately in this position by the makers, and if far from the correct position it will be found that one trace will fail to record owing to the displacement of the spot outside the camera recording slit.

Summary

A method of synchronous heart sound recording is described in which the standard Cossor-Robertson cardiograph is modified by introducing a second channel using the Clothier electronic switch.

Synchronisation of the tracings is automatic and requires no adjustment.

The alteration to the commercial instrument is simple and does not affect its use as a simple portable cardiograph.

We are indebted to Professor Crighton Bramwell for his interest in this work and to Messrs. A. C. Cossor Ltd., for their co-operation in undertaking the alteration to the Recorder Unit.

The total cost of the conversion, including fitting the terminals to the recorder unit, and the cost of materials for constructing the switch and external amplifier should not, in normal times, exceed £20. In addition a microphone is necessary.

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